83592

Access DB#_____

LB

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: BEN SACKEY Examiner #: 73489 Date: 1/4/03
Art Unit: 1626 Phone Number 305-6889 Serial Number: 10/077,154
Mail Box and Bldg/Room Location: CM1 3E11 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

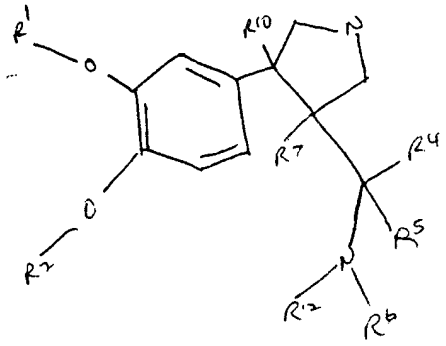
Title of Invention: Cyclic AMP-Specific phosphodiesterase inhibitors

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

A method of inhibiting IL-1β release by monocytes in a mammal comprising administering compound of formula (1).



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JAN - 3
(STIC)

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STAFF USE ONLY

Searcher: K. Fuller
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 1/6/03
Searcher Prep & Review Time: 20
Clerical Prep Time: _____
Online Time: 37

Type of Search

NA Sequence (#)_____
AA Sequence (#)_____
Structure (#) 2
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify)_____

PTO-1590 (8-01)

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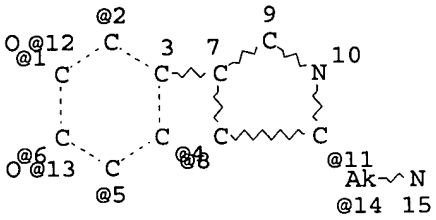
L9 HAS NO ANSWERS
L9 STR



VPA 12-2/1/6 U
VPA 13-4/5/6 U
VPA 14-11/8 U
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 11 3
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

=> s l9 ful
FULL SEARCH INITIATED 08:33:57 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 82898 TO ITERATE

100.0% PROCESSED 82898 ITERATIONS 67 ANSWERS
SEARCH TIME: 00.00.04

L11 67 SEA SSS FUL L9

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    FILE 'REGISTRY' ENTERED AT 08:31:59 ON 23 JAN 2003
L9                STRUC
L10           0 S L9
L11          67 S L9 FUL

     FILE 'CAPLUS' ENTERED AT 08:34:15 ON 23 JAN 2003
L12          26 S L11

     FILE 'REGISTRY' ENTERED AT 08:36:08 ON 23 JAN 2003

=> s l11 and pyrrolidin?
        361496 PYRROLIDIN?
L13          46 L11 AND PYRROLIDIN?

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     4.62     357.35

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -42.32

FILE 'CAPLUS' ENTERED AT 08:36:26 ON 23 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 23 Jan 2003  VOL 138 ISS 4
FILE LAST UPDATED: 22 Jan 2003  (20030122/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l13
L14          11 L13

=> d bib abs hitstr 1-11

L14  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:551608  CAPLUS
DN   137:125078
TI   Preparation of arylpyrrolidines as inhibitors of cyclic AMP-specific
     phosphodiesterase and as inhibitors of tumor necrosis factor release.
IN   Martins, Timothy J.; Fowler, Kerry W.; Odingo, Joshua; Kesicki, Edward A.;
     Oliver, Amy; Burgess, Laurence E.; Gaudino, John J.; Jones, Zachary S.;
     Newhouse, Bradley J.; Schlachter, Stephen T.
PA   ICOS Corporation, USA
SO   U.S., 128 pp., Cont.-in-part of U.S. 471,846.
     CODEN: USXXAM
DT   Patent
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LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6423710	B1	20020723	US 2000-717956	20001121
	US 6258833	B1	20010710	US 1999-471846	19991223
	US 6458787	B1	20021001	US 2001-847424	20010502
PRAI	US 1999-471846	A2	19991223		

OS MARPAT 137:125078
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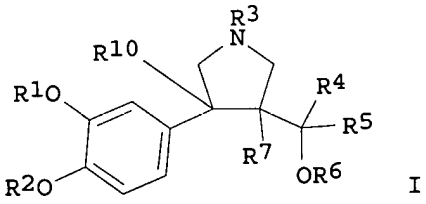


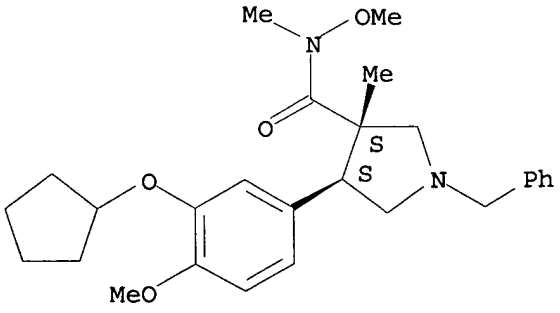
I

AB Title compds. [I; R1 = H, alkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, halocycloalkyl, (substituted) propargyl, allyl, etc.; R2 = H, Me, halomethyl, CHF2; R3 = CO2R7, COR7, NHCO2R7, aryl, heteroaryl, etc.; R4 = H, alkyl, haloalkyl, cycloalkyl, aryl; R5 = H, alkyl, alkynyl, haloalkyl, hydroxyalkyl, cycloalkyl, aryl; R6 = H, alkyl, COR7; R7 = (substituted) alkyl, alkylenearyl, cycloalkyl, heterocyclyl, heteroaryl, aryl, etc.; R10 = H, alkyl, haloalkyl, cycloalkyl, aryl, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, alkoxycarbonyl, CH2OH, etc.], were prepd. Thus, Me trans-3-acetyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylate in THF was added to MeMgBr in Et2O at 0.degree. followed by stirring at 0.degree. for 30 min. and at room temp. for 1 h to give 55% Me 4-(3-cyclopentyloxy-4-methoxyphenyl)-3-(1-OH-1-methylethyl)-3-methylpyrrolidine-1-carboxylate. I inhibited human PDE4 with IC50 = 700 pM to 15 .mu.M.

IT **347850-24-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

RN 347850-24-2 CAPLUS
CN 3-Pyrrolidinecarboxamide, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N-methoxy-N,3-dimethyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2001:489391 CAPLUS
DN 135:76878
TI Preparation of 3-tetrazolylpyrrolidines as cyclic AMP-specific phosphodiesterase inhibitors
IN Fowler, Kerry W.; Odingo, Joshua
PA Icos Corporation, USA
SO PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001047914	A1	20010705	WO 2000-US31813	20001117
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6294561	B1	20010925	US 2000-712092	20001114
	EP 1242407	A1	20020925	EP 2000-978823	20001117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2002032224	A1	20020314	US 2001-953512	20010914
	US 6455562	B2	20020924		
PRAI	US 1999-172068P	P	19991223		
	US 2000-712092	A1	20001114		
	WO 2000-US31813	W	20001117		

OS MARPAT 135:76878
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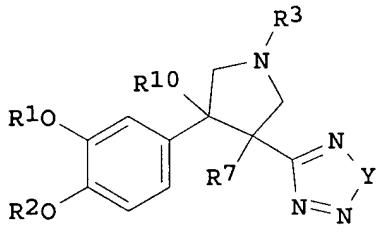

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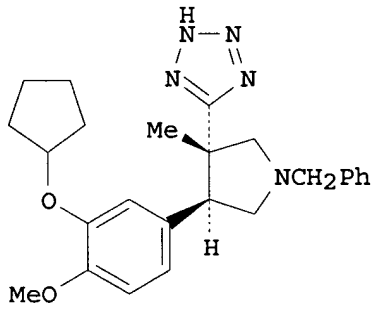


II

AB The title compds. [I; Y = O, NR4; R1 = alkyl, aralkyl, cycloalkyl, etc.; R2 = H, Me, halomethyl; R3 = CO2R7, COR7, alkyl, etc.; R4 = H, alkyl, haloalkyl, etc.; R7 = cycloalkyl, alkyl, heteroaryl, etc.; R10 = H, alkyl, haloalkyl, etc.] that are potent and selective inhibitors of PDE4, and are useful in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, were prepd. E.g., a multi-step synthesis of II which showed IC50 of 7.9 .mu.M against human recombinant PDE4, was given.

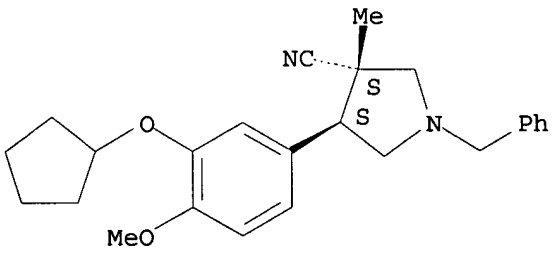
IT **347885-67-0P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3-tetrazolylpyrrolidines as cAMP-specific phosphodiesterase inhibitors)

RN 347885-67-0 CAPLUS

CN 3-Pyrrolidinecarbonitrile, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2003 ACS

AN 2001:489383 CAPLUS

DN 135:76790

TI Preparation of pyrrolidine derivatives as cyclic AMP-specific phosphodiesterase inhibitors

IN Martins, Timothy J.; Fowler, Kerry W.; Odingo, Joshua; Kesicki, Edward A.; Oliver, Amy; Burgess, Laurence E.; Gaudino, John J.; Jones, Zachary S.; Newhouse, Bradley J.; Schlachter, Stephen

PA Icos Corporation, USA

SO PCT Int. Appl., 551 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001047905	A1	20010705	WO 2000-US32401	20001128
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6258833	B1	20010710	US 1999-471846	19991223
	EP 1242400	A1	20020925	EP 2000-987999	20001128
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 6458787	B1	20021001	US 2001-847424	20010502
	NO 2002003008	A	20020820	NO 2002-3008	20020621
PRAI	US 1999-471846	A	19991223		
	WO 2000-US32401	W	20001128		

OS MARPAT 135:76790

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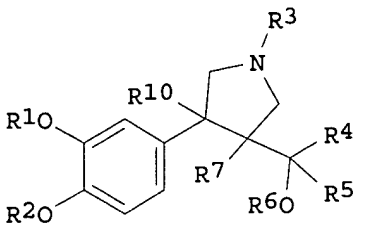

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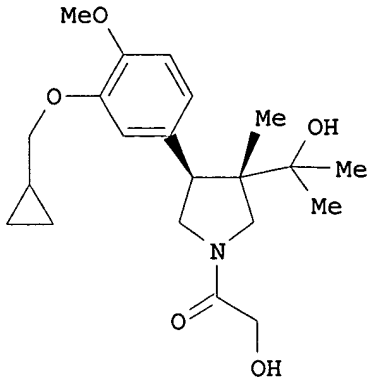


II

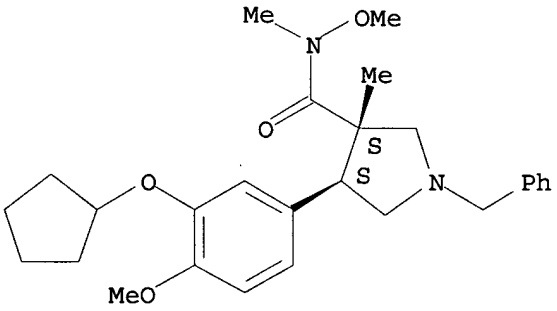
AB The title compds. [I; R1 = H, alkyl, aryl, etc.; R2 = H, Me, halo-substituted methyl; R3 = CO2R7, COR7, NHCO2R7, etc.; R4 = H, alkyl, haloalkyl, etc.; R5 = H, alkyl, alkynyl, etc.; R6 = H, alkyl, COR7; R7 = alkyl, cycloalkyl, heteroaryl, etc.; R10 = H, alkyl, aryl, etc.] that are potent and selective inhibitors of PDE4, and are useful in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, were prepd. E.g., a multi-step synthesis of II was presented. Biol. data (e.g., IC50 against PDE4 and EC50 against TNF.alpha. release) for compds. I were given.

IT **347850-24-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

RN 347850-24-2 CAPLUS

CN 3-Pyrrolidinecarboxamide, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N-methoxy-N,3-dimethyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2003 ACS

AN 2001:489364 CAPLUS

DN 135:92536

TI Preparation of pyrrolidines which inhibit cAMP-specific PDE

IN Martins, Timothy J.; Fowler, Kerry W.; Odingo, Joshua; Burgess, Laurence E.; Schlachter, Stephen T.

PA Icos Corp., USA

SO PCT Int. Appl., 143 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001047879	A1	20010705	WO 2000-US34116	20001215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6376489	B1	20020423	US 2000-731591	20001207
EP 1244619	A1	20021002	EP 2000-984450	20001215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002169196	A1	20021114	US 2002-77154	20020215
NO 2002003009	A	20020819	NO 2002-3009	20020621
PRAI US 1999-172023P	P	19991223		
US 2000-731591	A1	20001207		
WO 2000-US34116	W	20001215		

OS MARPAT 135:92536
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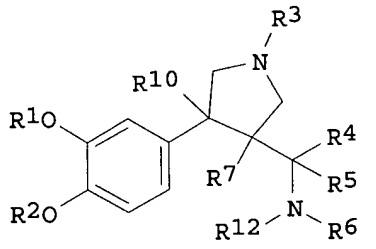

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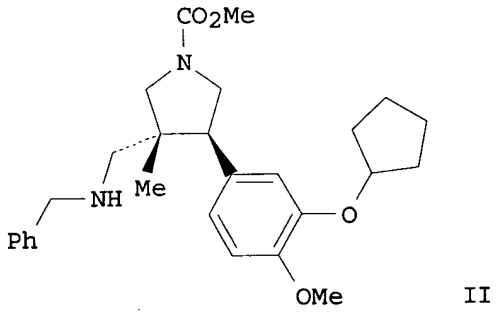


II

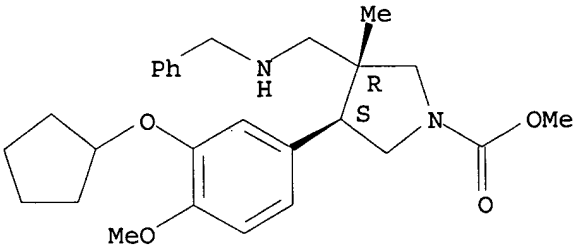
AB The title compds. [I; R1 = alkyl, aryl, heteroaryl, etc.; R2 = H, Me, halomethyl; R3 = CO2R7, COR7, alkyl, etc.; R4 = H, alkyl, haloalkyl, etc.; R5 = H, alkyl, alkynyl, etc.; R6, R12 = H, alkyl, aralkyl, etc.; R7 = alkyl, heteroaryl, aryl, etc.; R10 = H, alkyl, haloalkyl, etc.] that are potent and selective inhibitors of PDE4, and are useful in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, were prepd. E.g., a multi-step synthesis of II which showed IC50 of 1400.0x10-9 M against PDE4, and IC50 of 775.5x10-9 M against TNF.alpha. formation, was given.

IT **348077-95-2P 348077-96-3P 348077-97-4P**
348077-98-5P 348077-99-6P 348078-00-2P
348078-01-3P 348078-02-4P 348078-03-5P
348078-04-6P 348078-05-7P 348078-06-8P
348078-07-9P 348078-08-0P 348078-09-1P
348078-10-4P 348078-11-5P 348078-12-6P
348078-13-7P 348078-14-8P 348078-15-9P
348078-16-0P 348078-17-1P 348078-18-2P
348078-19-3P 348078-20-6P 348078-21-7P

348078-22-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)

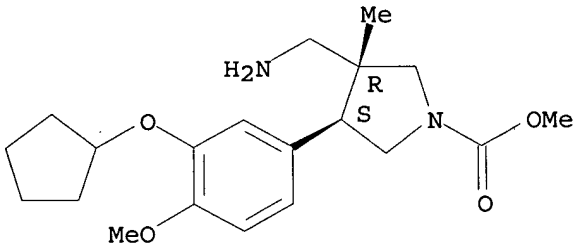
RN 348077-95-2 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[[(phenylmethyl)amino]methyl]-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



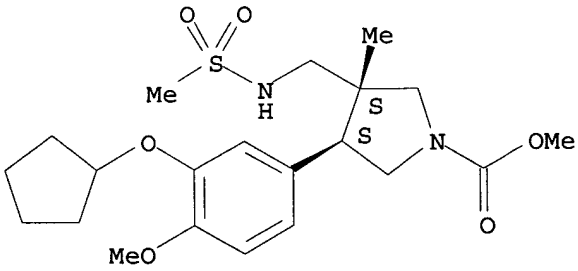
RN 348077-96-3 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 348077-97-4 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[[(methylsulfonyl)amino]methyl]-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

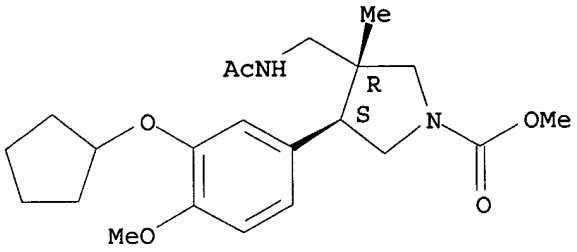
Absolute stereochemistry.



RN 348077-98-5 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[(acetylamino)methyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI)

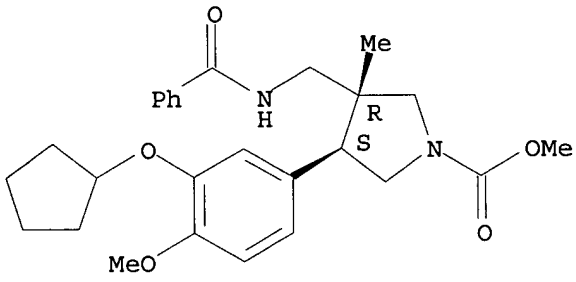
(CA INDEX NAME)

Absolute stereochemistry.



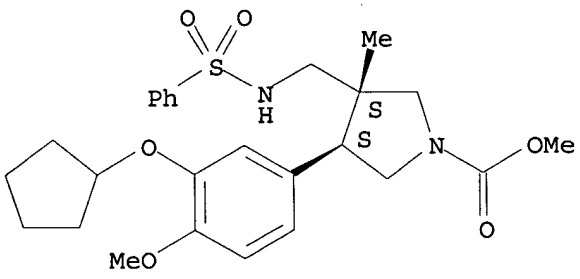
RN 348077-99-6 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[(benzoylamino)methyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



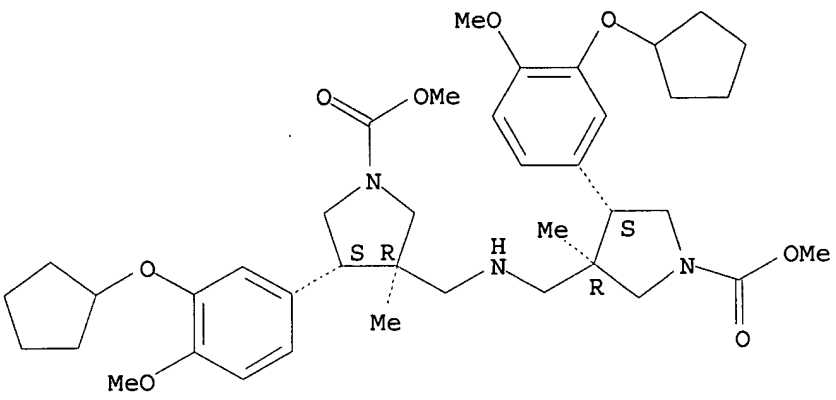
RN 348078-00-2 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[[(phenylsulfonyl)amino]methyl]-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



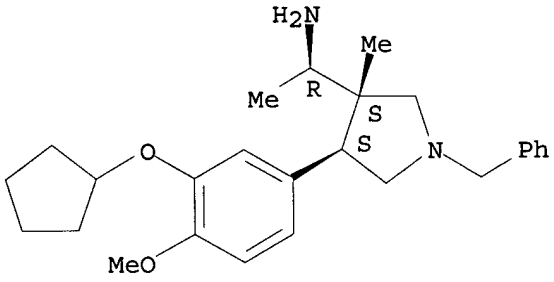
RN 348078-01-3 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3,3'-[iminobis(methylene)]bis[4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, dimethyl ester, (3R,3'R,4S,4'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



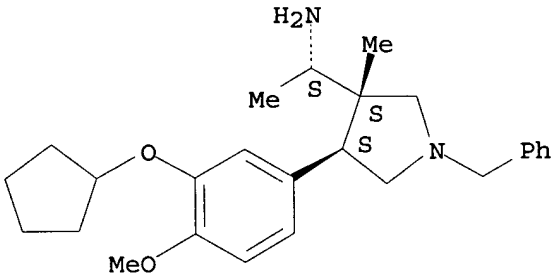
RN 348078-02-4 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-.alpha.,3-dimethyl-1-(phenylmethyl)-, (.alpha.R,3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



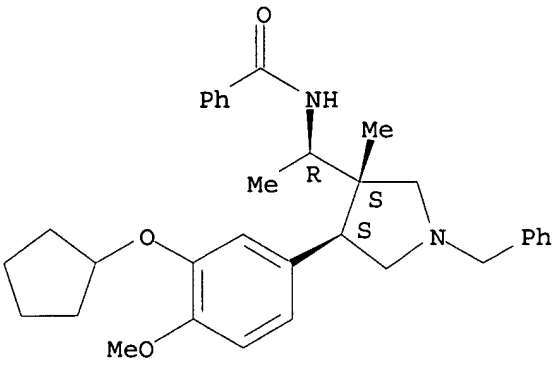
RN 348078-03-5 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-.alpha.,3-dimethyl-1-(phenylmethyl)-, (.alpha.S,3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



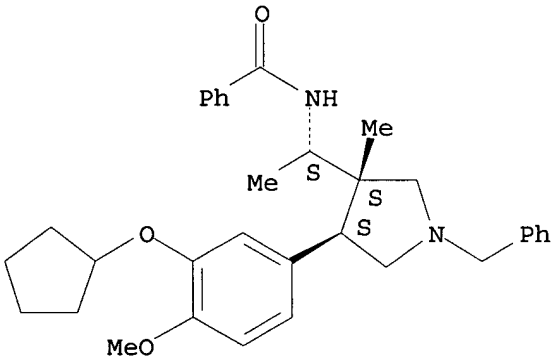
RN 348078-04-6 CAPLUS
CN Benzamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



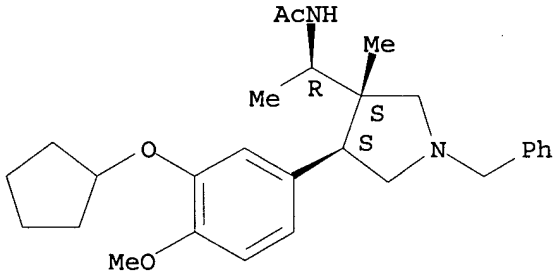
RN 348078-05-7 CAPLUS
CN Benzamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



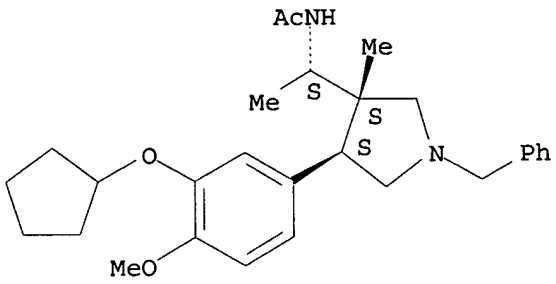
RN 348078-06-8 CAPLUS
CN Acetamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



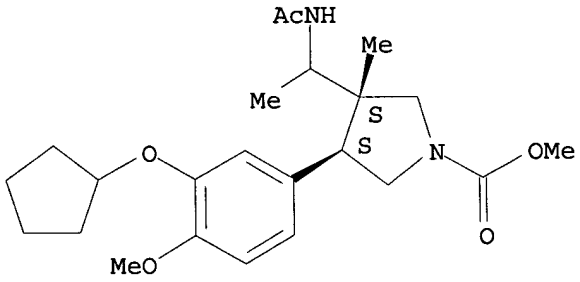
RN 348078-07-9 CAPLUS
CN Acetamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



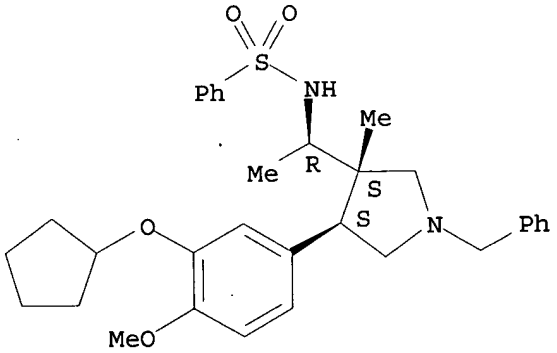
RN 348078-08-0 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[1-(acetylamino)ethyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



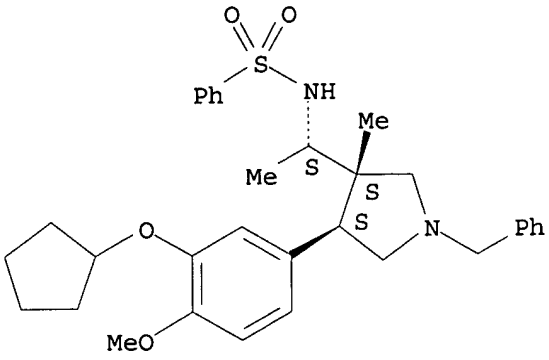
RN 348078-09-1 CAPLUS
CN Benzenesulfonamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



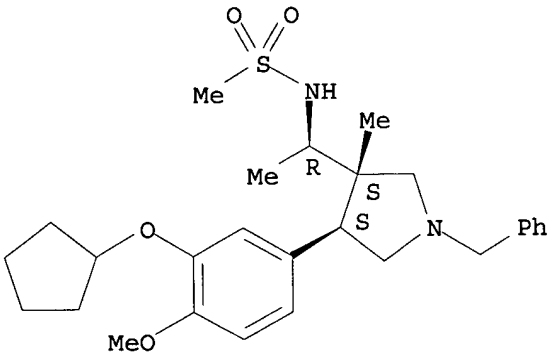
RN 348078-10-4 CAPLUS
CN Benzenesulfonamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



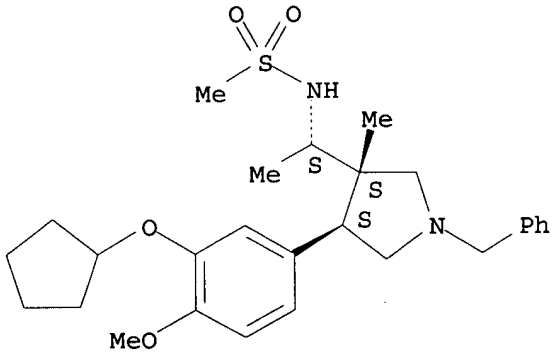
RN 348078-11-5 CAPLUS
CN Methanesulfonamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



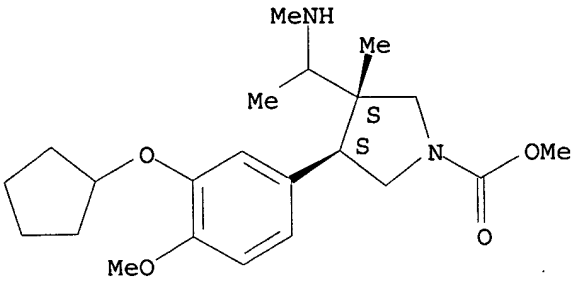
RN 348078-12-6 CAPLUS
CN Methanesulfonamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



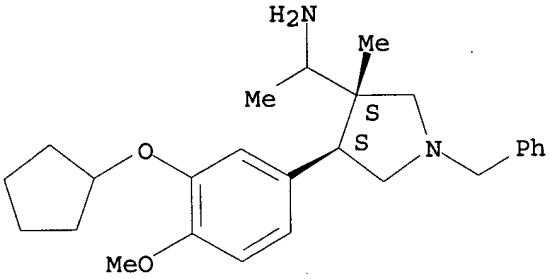
RN 348078-13-7 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[1-(methylamino)ethyl]-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



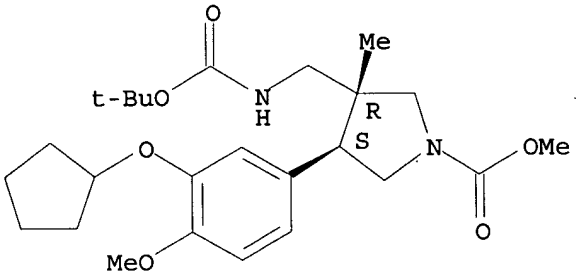
RN 348078-14-8 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-.alpha.,3-dimethyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



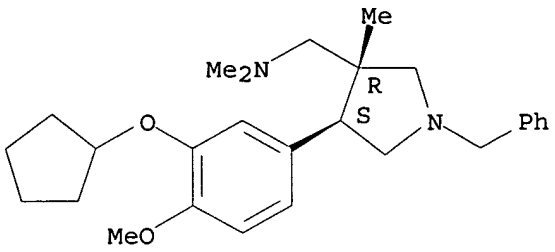
RN 348078-15-9 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



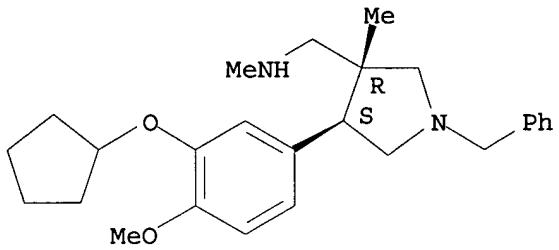
RN 348078-16-0 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N,N,3-trimethyl-1-(phenylmethyl)-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



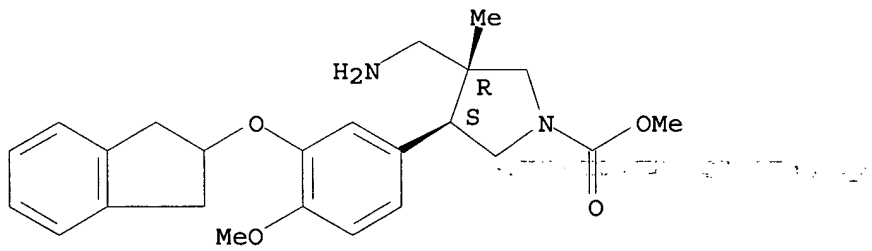
RN 348078-17-1 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N,3-dimethyl-1-(phenylmethyl)-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



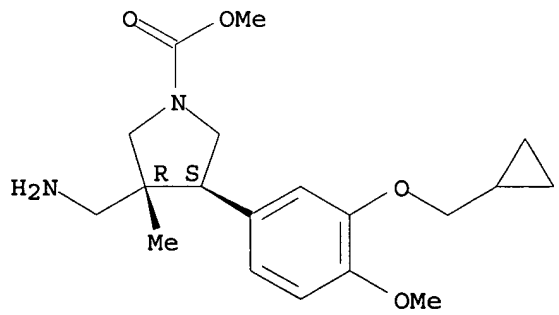
RN 348078-18-2 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminomethyl)-4-[3-[(2,3-dihydro-1H-inden-2-yl)oxy]-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

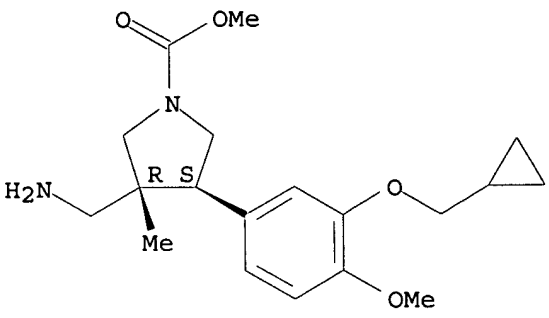
Absolute stereochemistry.



RN 348078-19-3 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminomethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

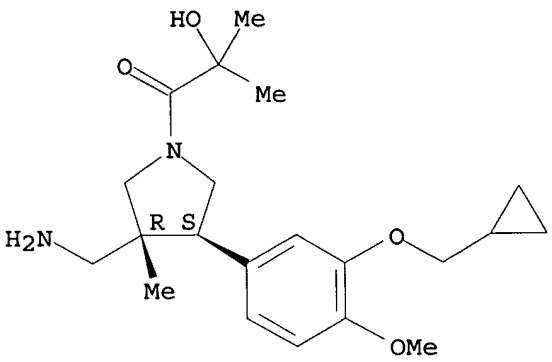
Absolute stereochemistry.





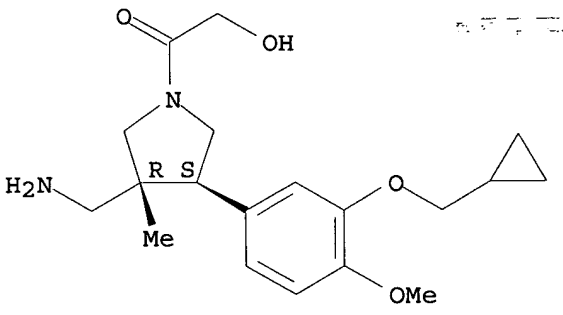
RN 348078-20-6 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-1-(2-hydroxy-2-methyl-1-oxopropyl)-3-methyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



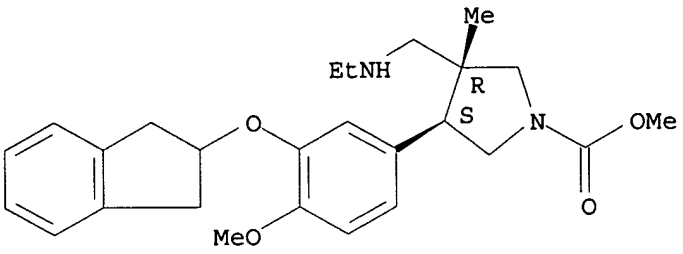
RN 348078-21-7 CAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-1-(hydroxyacetyl)-3-methyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 348078-22-8 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-[(2,3-dihydro-1H-inden-2-yl)oxy]-4-methoxyphenyl]-3-[(ethylamino)methyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2001:472663 CAPLUS
DN 135:61233
TI Preparation and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents
IN Fowler, Kerry W.; Oliver, Amy; Odingo, Joshua
PA Icos Corp., USA
SO PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001046136	A1	20010628	WO 2000-US42316	20001128
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6348602	B1	20020219	US 2000-716024	20001117
	EP 1242371	A1	20020925	EP 2000-992155	20001128
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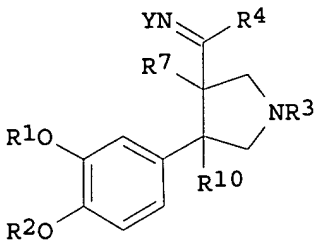
	US 2002065302	A1	20020530	US 2001-16910	20011214
	US 6500856	B2	20021231		
PRAI	US 1999-171955P	P	19991223		
	US 2000-716024	A1	20001117		
	WO 2000-US42316	W	20001128		

OS MARPAT 135:61233
GI



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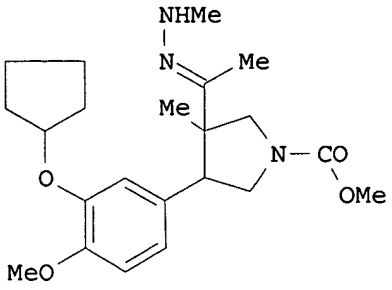


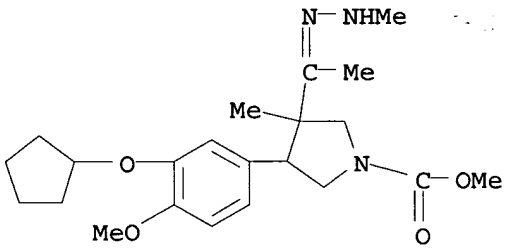
II

AB Pyrrolidine hydrazones and oximes, such as I [Y = OR5, NR5R6; R1 = alkyl, arylalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkynyl, etc.; R2 = H, Me, halomethyl; R3 = carboxyl, acyl, amido, aryl, heteroaryl, amidinyl; R4 = H, alkyl, haloalkyl, cycloalkyl, aryl; R5, R6 = H, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, etc.; R7 = alkyl, aryl, aminoalkyl, alkoxyalkyl, etc.; R10 = H, CH2OH, CHO, CN, NO2, alkyl, haloalkyl, cycloalkyl, aryl, acyl, sulfonyl, etc.], were prepd. as potent and selective inhibitors of PDE4 for use in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders. Thus, pyrrolidine hydrazone II was prepd. by reaction of the corresponding ketone with methylhydrazine by heating with a catalytic amt. of AcOH in MeOH for 36 h. The prepd. pyrrolidine hydrazones and oximes were tested for PDE4 and TNF.alpha. inhibiting activity.

IT **346408-85-3P 346408-86-4P 346408-87-5P 346408-88-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

RN 346408-85-3 CAPLUS

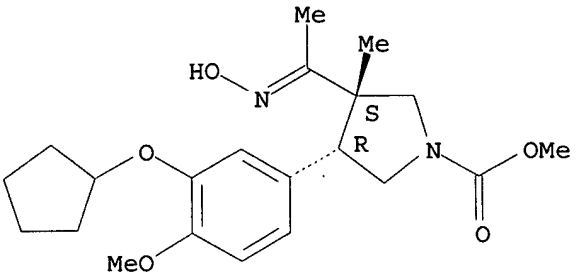
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[1-(methylhydrazono)ethyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 346408-86-4 CAPLUS

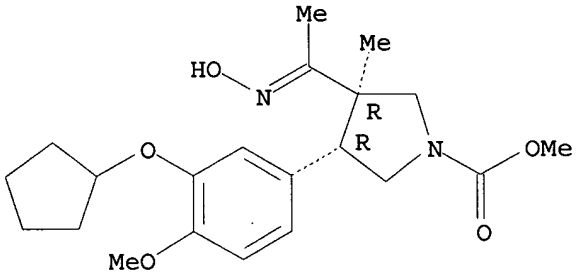
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[1-(hydroxyimino)ethyl]-3-methyl-, methyl ester, (3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



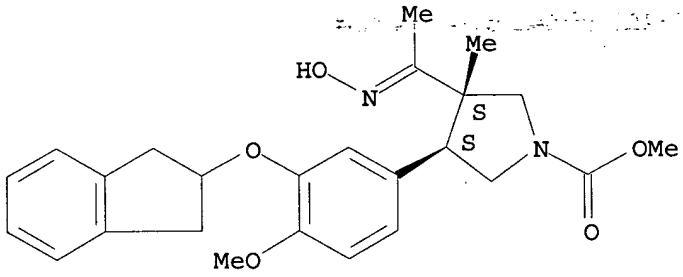
RN 346408-87-5 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[1-(hydroxyimino)ethyl]-3-methyl-, methyl ester, (3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 346408-88-6 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-[(2,3-dihydro-1H-inden-2-yl)oxy]-4-methoxyphenyl]-3-[1-(hydroxyimino)ethyl]-3-methyl-, methyl ester, (3R,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



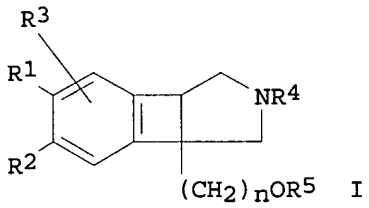
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2000:686286 CAPLUS
DN 133:252299
TI Benzo[3,4]cyclobuta[1,2-c]pyrrole derivatives as inhibitors of serotonin reuptake
IN Peglion, Jean-louis; Goument, Bertrand; Dessinges, Aimee; Millan, Mark; Rivet, Jean-michel; Dekeyne, Anne
PA Adir Et Compagnie, Fr.

SO Eur. Pat. Appl., 29 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1038873	A2	20000927	EP 2000-400812	20000324
	EP 1038873	A3	20001004		
	EP 1038873	B1	20020502		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	FR 2791345	A1	20000929	FR 1999-3811	19990326
	FR 2791345	B1	20010504		
	US 6153640	A	20001128	US 2000-533684	20000323
	CA 2301787	AA	20000926	CA 2000-2301787	20000324
	NO 2000001542	A	20000927	NO 2000-1542	20000324
	BR 2000001420	A	20001010	BR 2000-1420	20000324
	JP 2000290253	A2	20001017	JP 2000-83880	20000324
	JP 3256788	B2	20020212		
	ZA 2000001501	A	20001024	ZA 2000-1501	20000324
	CN 1274718	A	20001129	CN 2000-108332	20000324
	AT 216994	E	20020515	AT 2000-400812	20000324
PRAI	FR 1999-3811	A	19990326		

OS MARPAT 133:252299
GI

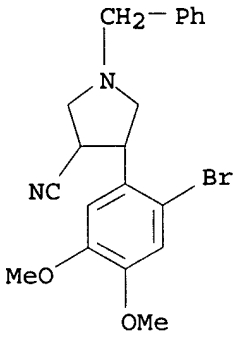


I

AB Benzocyclobutapyrroles I [R1-R3 = H, halogen, alkyl, alkenyl, alkynyl, OH, alkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aryloxy, arylalkoxy, trihaloalkyl, trihaloalkoxy, CN, NO2, O3SMe, O3SCF3, (un)substituted NH2, CO2H; R1R2, R1R3, R2R3 = atoms required to complete a benzekne, carbocyclic, or heterocyclic ring; R4 = H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylaklyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, hetyeroaryl, heteroarylalkyl; R5 = (un)substituted aryl, heteroaryl; n = 1-3] were prepd. for use as inhibitors of serotonin reuptake in treatment of depression, panic attack, obsessive-compulsive behavior, phobias, drug abuse, and anxiety. Thus, I [R1-R4 = H, R5 = 3,4-methylenedioxybenzyl, n = 1, II] was prepd. from PhCH2NHCH2CH2CN, 2-BrC6H4COCH2Br, and 3,4-methylenedioxyphenol in 10 steps. At 10 mg/kg s.c. in rats II increased serotonin levels by 226.3.+-.20.1%, dopamine levels by 54.8.+-.6.4%, and noradrenaline levels by 96.4.+-.7.8%.

IT **296228-42-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of benzo[3,4]cyclobuta[1,2-c]pyrrole derivs. as inhibitors of serotonin reuptake)

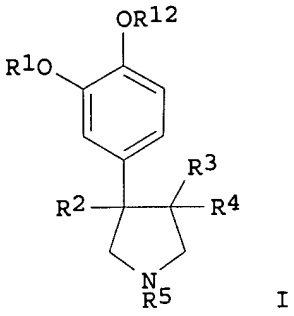
RN 296228-42-7 CAPLUS
CN 3-Pyrrolidinecarbonitrile, 4-(2-bromo-4,5-dimethoxyphenyl)-1-(phenylmethyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1995:812865 CAPLUS
DN 123:227981
TI Preparation of 3-(3,4-dioxyphenyl)pyrrolidines as type IV phosphodiesterase inhibitors for treatment of inflammatory diseases
IN Feldman, Paul Lawrence; Stafford, Jeffrey Alan
PA Glaxo Inc., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9508534	A1	19950330	WO 1994-US10678	19940920
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5665754	A	19970909	US 1993-123837	19930920
	CA 2171448	AA	19950330	CA 1994-2171448	19940920
	AU 9478396	A1	19950410	AU 1994-78396	19940920
	AU 685170	B2	19980115		
	EP 720600	A1	19960710	EP 1994-929281	19940920
	EP 720600	B1	20000712		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 09502979	T2	19970325	JP 1994-509907	19940920
	AT 194593	E	20000715	AT 1994-929281	19940920
	ES 2149888	T3	20001116	ES 1994-929281	19940920
PRAI	US 1993-123837	A	19930920		
	WO 1994-US10678	W	19940920		

OS MARPAT 123:227981
GI



I

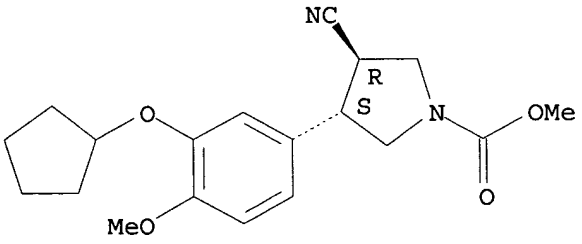
AB Title compds. I (R1 = alkyl, haloalkyl, cycloalkyl bridged polycycloalkyl, aryl, heteroaryl, etc.; R2 = H, alkyl, haloalkyl, cycloalkyl, aryl, HOVH2, CHO, NC, etc.; R3 = NC, O2N, CHO, alkyl-CO, cycloalkyk-CO, etc.; R4 = H, alkyl, haloalkyl, cycloalkyl, alkyl-CO, haloalkyl-CO, etc.; R5 = NC, R10O2S, R11XC where R10 = alkyl, cycloalkyl, F3C, aryl, etc.. R11 = H, haloalkyl, aryl, etc.; R12 = C1-3 alkyl, cyclopropyl, C1-3 haloalkyl, X = O, S), are prepd. To trimethylphosphonoacetate was added Lithiumbis(trimethylsilyl)amide and 3-(cyclopentyloxy)-4-methoxybenzaldehyde to give Me (E)-3-(3-cyclopentoxy-4-methoxyphenyl)-2-propenoate. A similar prepd compd. cis-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)-1-(phenylmethyl)pyrrolidine was treated with di-tert-Bu dicarbonate to give I (R1 = cyclopentyl, R2 = R4 = H, R3 = MeO2C, R5 Me3CO2C, R12 = Me). In test for phosphodiesterase inhibitory activity the IC50 of I was 100pM-200.mu.M. I are also claimed for treatment of autoimmune diseases, elevated cytokinin levels, etc. Pharmaceutical compns. comprising I are given.

IT **168169-43-5P 168169-63-9P 168169-64-0P 168169-65-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-(3,4-dioxyphenyl)pyrrolidines as type IV phosphodiesterase inhibitors for treatment of inflammatory diseases)

RN 168169-43-5 CAPLUS

CN 1-Pyrrolidinecarboxylic acid, 3-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-, methyl ester, trans- (9CI) (CA INDEX NAME)

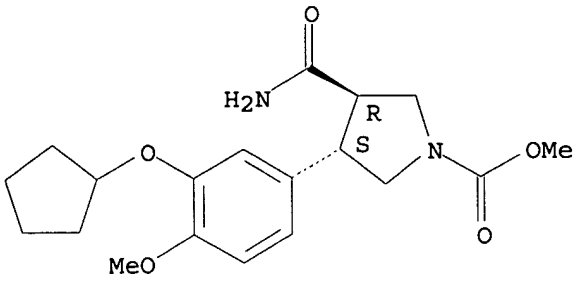
Relative stereochemistry.



RN 168169-63-9 CAPLUS

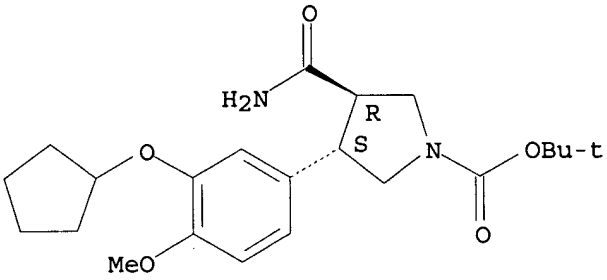
CN 1-Pyrrolidinecarboxylic acid, 3-(aminocarbonyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-, methyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



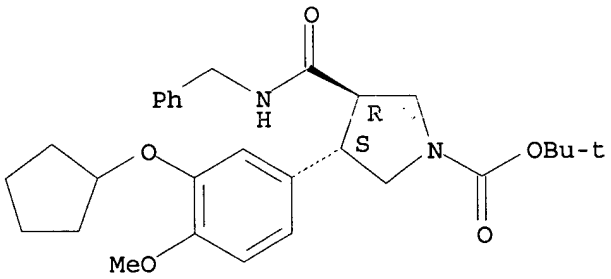
RN 168169-64-0 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminocarbonyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-, 1,1-dimethylethyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



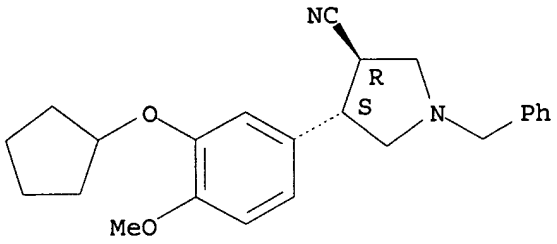
RN 168169-65-1 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4-[[(phenylmethyl)amino]carbonyl]-, 1,1-dimethylethyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



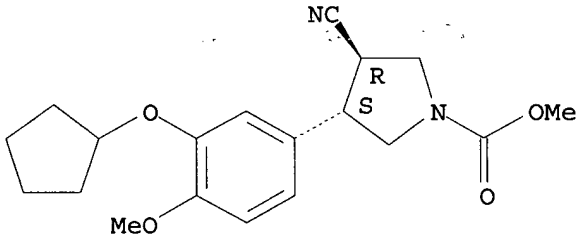
IT **168170-12-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3-(3,4-dioxyphenyl)pyrrolidines as type IV phosphodiesterase inhibitors for treatment of inflammatory diseases)
RN 168170-12-5 CAPLUS
CN 3-Pyrrolidinecarbonitrile, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-(phenylmethyl)-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



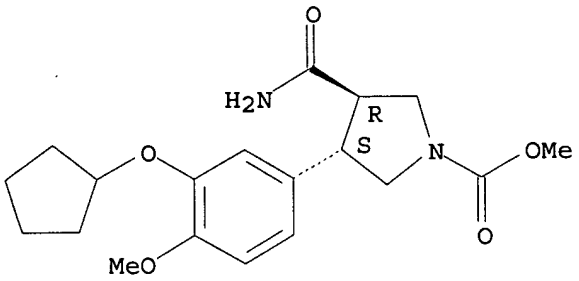
L14 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1995:796297 CAPLUS
DN 123:339605
TI Phosphodiesterase type IV (PDE IV) inhibition. Synthesis and evaluation of a series of 1,3,4-trisubstituted pyrrolidines
AU Stafford, Jeffrey A.; Valvano, Nicole L.; Feldman, Paul L.; Brawley, E. Sloan; Cowan, David J.; Domanico, Paul L.; Leesnitzer, Michael A.; Rose, Dubley A.; Stimpson, Stephen A.; et al.
CS Glaxo Wellcome Research Institute, Research Triangle Park, NC, 27709, USA
SO Bioorganic & Medicinal Chemistry Letters (1995), 5(17), 1977-82
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
AB Structure-activity relationships within a series of 1,3,4-trisubstituted pyrrolidines, novel and selective inhibitors of cAMP-specific phosphodiesterase (PDE IV), are discussed.
IT **168169-43-5P 168169-63-9P 168169-64-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of 1,3,4-trisubstituted pyrrolidines as selective inhibitors of cAMP-specific phosphodiesterase)
RN 168169-43-5 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-, methyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



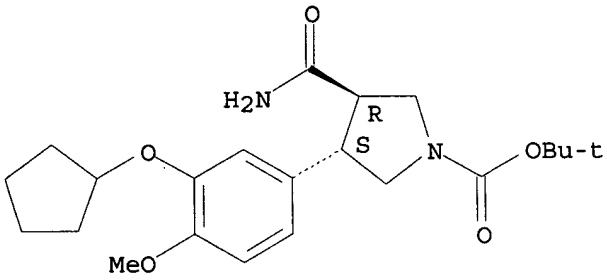
RN 168169-63-9 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminocarbonyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-, methyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



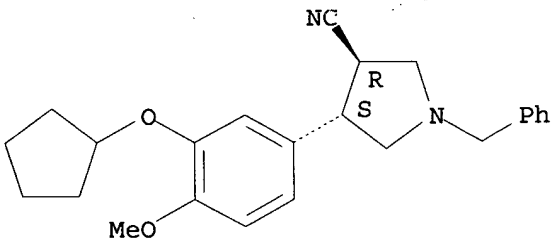
RN 168169-64-0 CAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminocarbonyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-, 1,1-dimethylethyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **168170-12-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of 1,3,4-trisubstituted pyrrolidines as selective inhibitors of cAMP-specific phosphodiesterase)
RN 168170-12-5 CAPLUS
CN 3-Pyrrolidinecarbonitrile, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-(phenylmethyl)-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



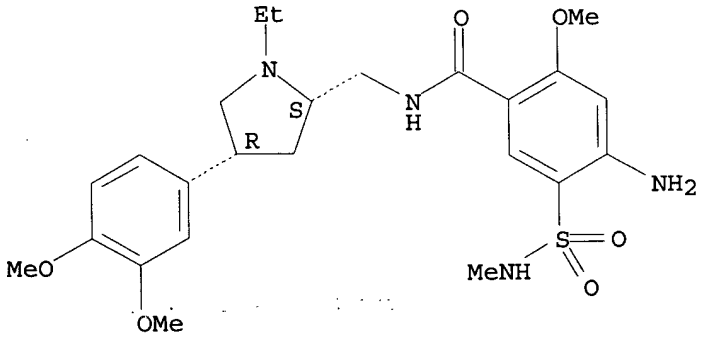
L14 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1990:584867 CAPLUS
DN 113:184867
TI Optically active benzamides as predictive tools for mapping the dopamine D2 receptor
AU Rognan, Didier; Sokoloff, Pierre; Mann, Andre; Martres, Marie Pascale; Schwartz, Jean Charles; Costentin, Jean; Wermuth, Camille Georges
CS Cent. Neurochim., CNRS, Strasbourg, 67084, Fr.
SO European Journal of Pharmacology, Molecular Pharmacology Section (1990), 189(1), 59-70
CODEN: EJPPET; ISSN: 0922-4106

DT Journal
LA English
AB Substituent variations on the pyrrolidinyl nitrogen of sulpiride, a selective D2 dopamine antagonist, showed that in vitro and in vivo activities are concd. in the (S) optical series for N-alkyl analogs and in the (R) series for N-benzyl analogs. To account for these unusual structure-activity relationships, a pharmacophoric model was built from the crystallog. structure of (-)-piquindone and extended to other D2 antagonists. This model considers the lone pair orientation of the basic nitrogen rather than its spatial location. Two distinct active conformations for benzamides were defined, corresponding to the (S) and (R) series. An extended pharmacophore is then proposed involving four main anchoring areas: (1) an arom. site Ar1, (2) a tertiary nitrogen with its lone pair orthogonal to the Ar1 plane, (3) a dipole .DELTA.1 coplanar to the Ar1 ring, and (4) three sites for the N-substituent, including a small hydrophobic pocket and two different arom. binding sites Ar2 and Ar3. To probe the predictive value of this model, structures were designed and several compds. were synthesized and tested as inhibitors of [125I]iodosulpride binding to rat striatal membranes and as antagonists of apomorphine-induced stereotyped behavior in mice.

IT **129977-32-8 129977-33-9 129989-79-3**, DO 766
RL: BIOL (Biological study)
(dopaminergic receptor affinity for, structure in relation to)

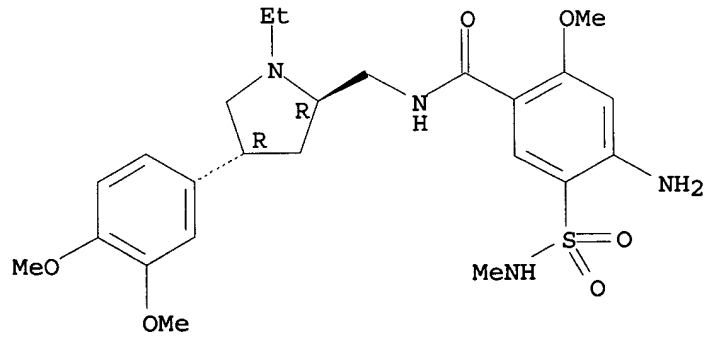
RN 129977-32-8 CAPLUS
CN Benzamide, 4-amino-N-[[4-(3,4-dimethoxyphenyl)-1-ethyl-2-pyrrolidinyl]methyl]-2-methoxy-5-[(methylamino)sulfonyl]-, cis- (9CI) (CA INDEX NAME)

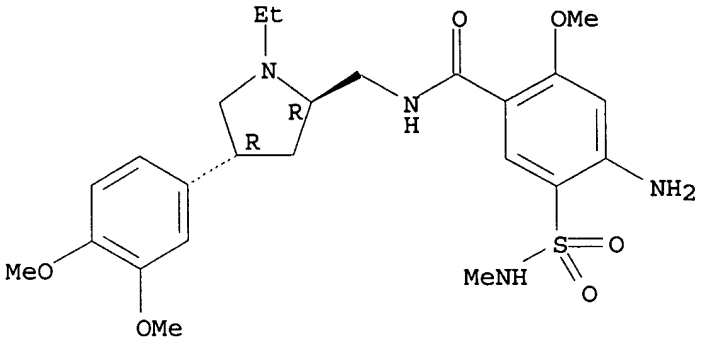
Relative stereochemistry.



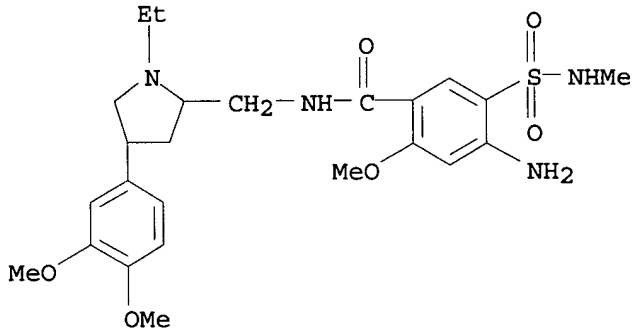
RN 129977-33-9 CAPLUS
CN Benzamide, 4-amino-N-[[4-(3,4-dimethoxyphenyl)-1-ethyl-2-pyrrolidinyl]methyl]-2-methoxy-5-[(methylamino)sulfonyl]-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.





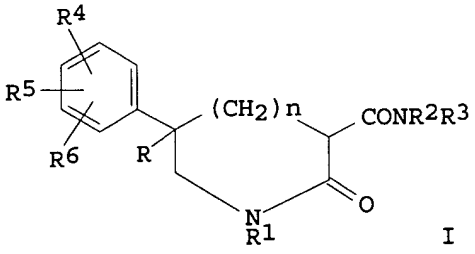
RN 129989-79-3 CAPLUS
CN Benzamide, 4-amino-N-[[4-(3,4-dimethoxyphenyl)-1-ethyl-2-pyrrolidinyl]methyl]-2-methoxy-5-[(methylamino)sulfonyl]- (9CI) (CA INDEX NAME)



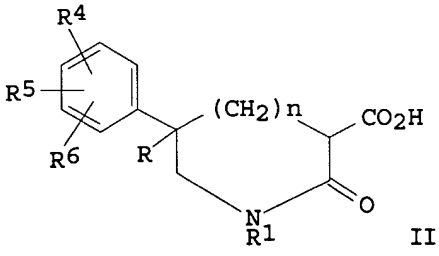
L14 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1978:152411 CAPLUS
DN 88:152411
TI Heterocyclic amide derivatives
IN Yuki, Hiroshi; Setoguchi, Nobuo
PA Yoshitomi Pharmaceutical Industries, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 52156859	A2	19771227	JP 1976-72457	19760618
PRAI	JP 1976-72457		19760618		

GI



I

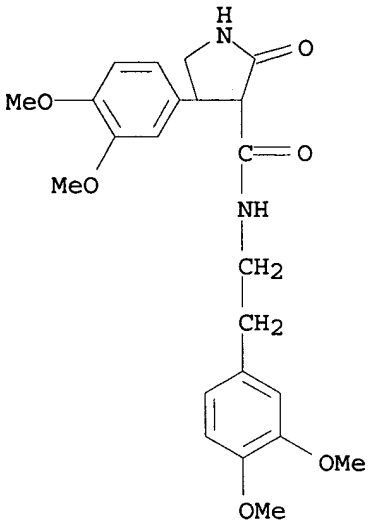


II

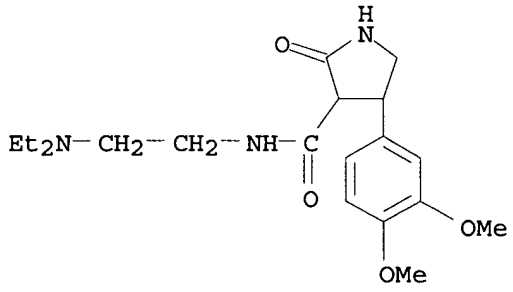
AB Thirty-five title derivs. I [R = H, Ph, pyridyl; R1 = H, alkyl, aralkyl; R2, R3 = H, alkyl, aralkyl, Ph, etc.; R2R3N may form a ring; R4, R5, R6 = H, alkyl, alkoxy, halo; R4 and R5 may be bound to form a methylenedioxy group;; n = 0, 1] were prepd. by reaction of II or their CO2H reactive derivs. with R2R3NH. I had antihypertensive, vasodilating, antithrombotic, analgesic, and anti-inflammatory activities (no data). Thus, a mixt., of 9.2 g 3-(ethoxycarbonyl)-4-phenyl-2-pyrrolidone and 4.2 g piperidine in xylene was refluxed 46 h to give 8 g I (R = R1 = R4 = R5 = R6 = H, R2R3N = piperidino, n = 0).

IT **62836-35-5P 66158-03-0P 66158-04-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 62836-35-5 CAPLUS
CN 3-Pyrrolidinecarboxamide, 4-(3,4-dimethoxyphenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-oxo- (9CI) (CA INDEX NAME)

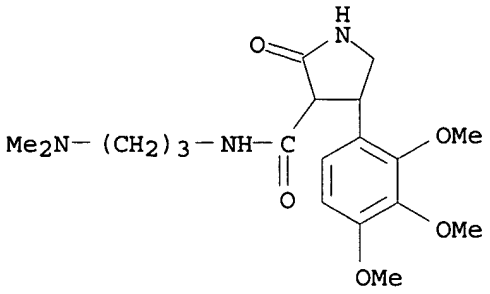


RN 66158-03-0 CAPLUS
CN 3-Pyrrolidinecarboxamide, N-[2-(diethylamino)ethyl]-4-(3,4-dimethoxyphenyl)-2-oxo-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

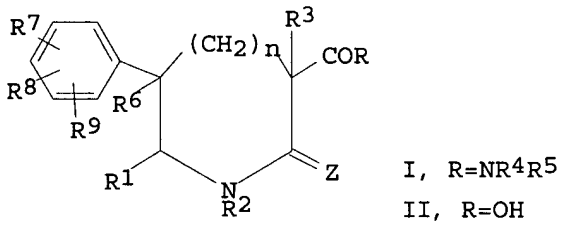
RN 66158-04-1 CAPLUS
CN 3-Pyrrolidinecarboxamide, N-[3-(dimethylamino)propyl]-2-oxo-4-(2,3,4-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1977:406018 CAPLUS
DN 87:6018
TI Amides
IN Yuki, Hiroshi; Setoguchi, Shinro
PA Yoshitomi Pharmaceutical Industries, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 51131870	A2	19761116	JP 1975-9020	19750120
PRAI	JP 1975-9020		19750120		

GI

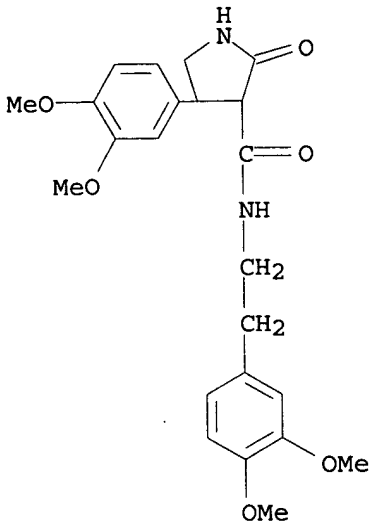


I, R=NR4R5
II, R=OH

AB Amides I (R1, R3 = H, alkyl; R2 = H, alkyl, aralkyl; R4, R5 = H, NH2, alkyl, dialkylamino, dialkylaminoalkyl, (substituted) Ph, aralkyl, PhNH, pyridyl, N-alkyl- or aralkyl 4-piperidyl; R4R5N may form a ring; R6 = H, (substituted) Ph; R7, R8, R9 = H, halo, alkyl, alkoxy; or R7R8 = OCH2O; Z = O, S; n = 0, 1) were prepd.,by amidation of II or their CO2H reactive derivs. with HNR4R5. I are hypotensives, psychotropic agents, analgesics, or antiinflammatory agents (no data). Thus, reflux of a mixt. of 9.2 g 3-ethoxycarbonyl-4-phenyl-2-pyrrolidone and 4.2 g piperidine in xylene 46 h gave 8 g 4-phenyl-3-piperidinocarbonyl-2-pyrrolidone. Among 19 addnl. I prepd. were N-(2-dimethylaminoethyl)-1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinecarboxamide-HCl, 3-(4-benzylpiperazin-1-ylcarbonyl)-1-methyl-4,4-diphenyl-2-pyrrolidone-HCl, 3-(4-benzylpiperazin-1-ylcarbonyl)-1-methyl-5,5-diphenyl-2-piperidone, and 4-phenyl-3-(4-methylpiperazin-1-ylcarbonyl)-2-pyrrolidone-HCl.

IT **62836-35-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 62836-35-5 CAPLUS
CN 3-Pyrrolidinecarboxamide, 4-(3,4-dimethoxyphenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-oxo- (9CI) (CA INDEX NAME)


H
N
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MeO
MeO
C
O
NH
CH2
CH2
OMe
OMe

=> FILE REG
FILE 'REGISTRY' ENTERED AT 11:37:06 ON 06 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 3 JAN 2003 HIGHEST RN 478133-28-7
DICTIONARY FILE UPDATES: 3 JAN 2003 HIGHEST RN 478133-28-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> FILE HCAPLUS
FILE 'HCAPLUS' ENTERED AT 11:37:12 ON 06 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 6 Jan 2003 VOL 138 ISS 2
FILE LAST UPDATED: 5 Jan 2003 (20030105/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> D QUE
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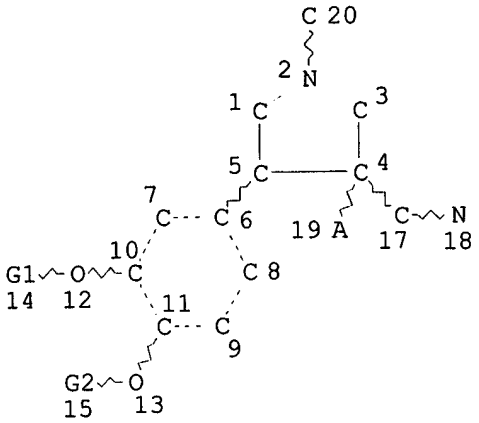

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L10 34 SEA FILE=REGISTRY SSS FUL L8
L11 5 SEA FILE=HCAPLUS ABB=ON L10

5 CA references
no CAOLD references

=> D L11 1-5 ALL HITSTR

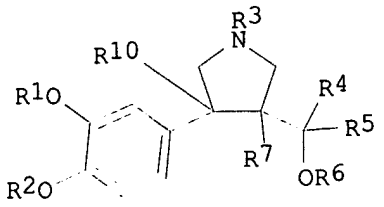
L11 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:551608 HCAPLUS
DN 137:125078
TI Preparation of arylpyrrolidines as inhibitors of cyclic AMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release.
IN Martins, Timothy J.; Fowler, Kerry W.; Odingo, Joshua; Kesicki, Edward A.; Oliver, Amy; Burgess, Laurence E.; Gaudino, John J.; Jones, Zachary S.; Newhouse, Bradley J.; Schlachter, Stephen T.
PA ICOS Corporation, USA
SO U.S., 128 pp., Cont.-in-part of U.S. 471,846.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-535
ICS A61K031-495; C07D413-00; C07D207-06
NCL 514231500
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

applicants

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6423710	B1	20020723	US 2000-717956	20001121
	US 6258833	B1	20010710	US 1999-471846	19991223
	US 6458787	B1	20021001	US 2001-847424	20010502

KATHLEEN FULLER EIC 1700/PARKER LAW 308-4290

PRAI US 1999-471846 A2 19991223
OS MARPAT 137:125078
GI



I

AB Title compds. [I; R1 = H, alkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, halocycloalkyl, (substituted) propargyl, allyl, etc.; R2 = H, Me, halomethyl, CHF2; R3 = CO2R7, COR7, NHCO2R7, aryl, heteroaryl, etc.; R4 = H, alkyl, haloalkyl, cycloalkyl, aryl; R5 = H, alkyl, alkynyl, haloalkyl, hydroxyalkyl, cycloalkyl, aryl; R6 = H, alkyl, COR7; R7 = (substituted) alkyl, alkylenearyl, cycloalkyl, heterocyclyl, heteroaryl, aryl, etc.; R10 = H, alkyl, haloalkyl, cycloalkyl, aryl, alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, alkoxycarbonyl, CH2OH, etc.], were prepd. Thus, Me trans-3-acetyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylate in THF was added to MeMgBr in Et2O at 0.degree. followed by stirring at 0.degree. for 30 min. and at room temp. for 1 h to give 55% Me 4-(3-cyclopentyloxy-4-methoxyphenyl)-3-(1-OH-1-methylethyl)-3-methylpyrrolidine-1-carboxylate. I inhibited human PDE4 with IC50 = 700 pM to 15 .mu.M.

ST arylpyrrolidine prepn PDEIV inhibitor; pyrrolidine aryl prepn phosphodiesterase adenosine cyclic monophosphate specific inhibitor; TNF prodn inhibitor arylpyrrolidine

IT Human
(prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

IT 9036-21-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IV; prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

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347847-74-9P 347847-77-2P 347848-85-5P 347848-87-7P 347848-89-9P
347848-91-3P 347848-93-5P 347849-81-4P 347849-82-5P 347849-83-6P
347849-84-7P 347850-51-5P 347850-52-6P 347850-60-6P 347850-63-9P
347850-68-4P 347850-69-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

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(prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

IT 60-12-8, 2-Phenylethanol 74-89-5, Methylamine, reactions 75-16-1, Methylmagnesium bromide 78-93-3, 2-Butanone, reactions 79-22-1, Methyl chloroformate 98-52-2, 4-tert-Butylcyclohexanol 100-46-9, Benzylamine, reactions 101-55-3 103-63-9, 2-Phenethyl bromide 104-52-9, 3-Phenylpropyl chloride 106-96-7, Propargyl bromide 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 327-56-0, D-Norleucine 332-48-9 395-33-5, 2-(4-Fluorophenyl)-2-hydroxyacetic acid 453-20-3, 3-Hydroxytetrahydrofuran 455-13-0, 4-Iodobenzotrifluoride 497-36-9, endo-Norborneol 500-22-1, Pyridine-3-carboxaldehyde 589-91-3, 4-Methylcyclohexanol 597-43-3 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 623-03-0 624-95-3, 3,3-Dimethylbutanol 626-55-1, 3-Bromopyridine 766-00-7, 2-Cyclopentylethanol 767-05-5, Cyclopentanepropanol 768-22-9, Indene oxide 825-51-4, Decahydronaphthalen-2-ol 872-85-5, Pyridine-4-carboxaldehyde 917-54-4, Methyllithium 1003-03-8, Cyclopentylamine 1121-60-4, Pyridine-2-carboxaldehyde 1129-78-8 1138-80-3 1168-87-2 1504-58-1, 3-Phenyl-2-propyn-1-ol 1638-63-7 1716-42-3 1738-86-9 1738-87-0 1849-02-1 2344-70-9, 4-Phenyl-2-butanol 2433-14-9, Bicyclohexyl-4-ol 2495-35-4, Benzyl acrylate 2566-44-1, 2-Cyclopropylethanol 2578-84-9 2578-85-0 2746-14-7, 1-Methylcyclopropanemethanol 3034-53-5, 2-Bromothiazole 3047-32-3, 3-Ethyl-3-oxetanemethanol 3313-85-7, Bicyclo[3.1.0]hex-6-ylmethanol 3355-28-0, 1-Bromo-2-butyne 3401-36-3 3642-91-9 3655-05-8 3699-66-9, Triethyl 2-phosphonopropionate 4254-29-9, 2-Indanol 4467-55-4 4830-93-7, 1-Chloro-4-phenylbutane 5437-45-6, Benzyl bromoacetate 5781-53-3, Methyl oxalyl chloride 6226-39-7, Bicyclo[4.1.0]hept-7-ylmethanol 6346-05-0, 3-Benzyloxy-4-methoxybenzaldehyde 7051-34-5, Bromomethylcyclopropane 7326-19-4, (R)-2-Hydroxy-3-phenylpropanoic acid 10512-93-3 10553-78-3 13748-90-8, (S)-2-Hydroxy-4-methylpentanoic acid 13831-31-7, Acetoxyacetyl chloride 14300-33-5, Dicyclopropylcarbinol 15030-72-5 15733-63-8, 1-Chloro-5-phenylpentane 15833-61-1, Tetrahydrofuran-3-methanol 17623-96-0 18217-00-0 19079-75-5 19810-31-2, Benzyloxyacetyl chloride 20312-36-1 24181-97-3 26782-71-8 29667-46-7 30129-18-1 31062-20-1 31729-66-5, 1-Phenylcyclopropylmethanol 33606-34-7, 2-(Tetrahydrofuran-2-yl)ethanol 34841-06-0, 3-Bromo-4-methoxybenzaldehyde 35272-15-2, 2-Methylthiazole-4-carboxylic acid 36394-75-9, (S)-2-Acetoxypropionyl chloride 37729-18-3, [1,1'-Biphenyl]-4-ethanol 40635-66-3 47173-80-8 52235-17-3 56539-66-3, 3-Methoxy-3-methylbutanol 57070-76-5 59115-90-1, 1-Phenylcyclopentylmethanol 60656-87-3,

Benzyloxyacetaldehyde 62965-10-0 67387-76-2, 3-Cyclopentyloxy-4-methoxybenzaldehyde 69595-02-4 69901-85-5 82490-61-7 86087-23-2, (S)-3-Hydroxytetrahydrofuran 90192-47-5 93102-05-7 97673-82-0 108104-24-1 116561-26-3 204119-59-5 205880-21-3 347850-53-7 347850-65-1 347850-66-2 443790-86-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD

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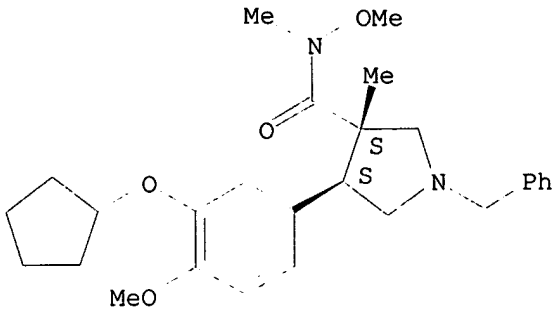
IT **347850-24-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of arylpyrrolidines as inhibitors of cAMP-specific phosphodiesterase and as inhibitors of tumor necrosis factor release)

RN 347850-24-2 HCAPLUS

CN 3-Pyrrolidinecarboxamide, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N-methoxy-N,3-dimethyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:489391 HCAPLUS
DN 135:76878
TI Preparation of 3-tetrazolylpyrrolidines as cyclic AMP-specific phosphodiesterase inhibitors
IN Fowler, Kerry W.; Odingo, Joshua
PA Icos Corporation, USA
SO PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-04
ICS C07D413-04; A61K031-41; C07D403-04; C07D257-00; C07D207-00; C07D413-04; C07D273-00; C07D207-00
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001047914	A1	20010705	WO 2000-US31813	20001117
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6294561	B1	20010925	US 2000-712092	20001114
	EP 1242407	A1	20020925	EP 2000-978823	20001117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2002032224	A1	20020314	US 2001-953512	20010914
	US 6455562	B2	20020924		
PRAI	US 1999-172068P	P	19991223		
	US 2000-712092	A1	20001114		
	WO 2000-US31813	W	20001117		

OS MARPAT 135:76878
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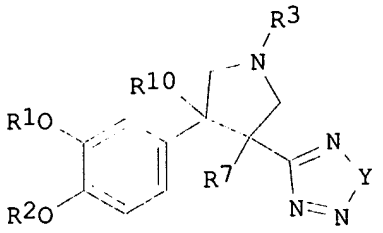

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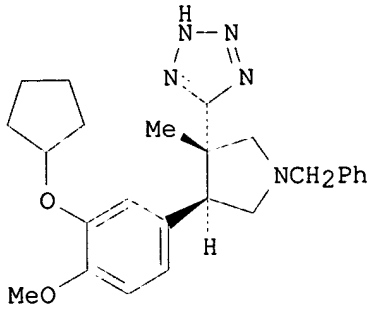


II

AB The title compds. [I; Y = O, NR4; R1 = alkyl, aralkyl, cycloalkyl, etc.; R2 = H, Me, halomethyl; R3 = CO2R7, COR7, alkyl, etc.; R4 = H, alkyl, haloalkyl, etc.; R7 = cycloalkyl, alkyl, heteroaryl, etc.; R10 = H, alkyl, haloalkyl, etc.] that are potent and selective inhibitors of PDE4, and are useful in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, were prepd. E.g., a multi-step synthesis of II which showed IC50 of 7.9 .mu.M against human recombinant PDE4, was given.

ST tetrazolylpyrrolidine prepn phosphodiesterase adenosine cyclic monophosphate specific inhibitor; pyrrolidine tetrazolyl prepn phosphodiesterase adenosine cyclic monophosphate specific inhibitor

IT 9036-21-9, phosphodiesterase IV
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(IV; prepn. of 3-tetrazolylpyrrolidines as cAMP-specific phosphodiesterase inhibitors)

IT 347885-63-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-tetrazolylpyrrolidines as cAMP-specific phosphodiesterase inhibitors)

IT 3699-66-9 67387-76-2, 3-Cyclopentyloxy-4-methoxybenzaldehyde 90319-52-1, (R)-4-Phenyloxazolidin-2-one 93102-05-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 3-tetrazolylpyrrolidines as cAMP-specific phosphodiesterase inhibitors)

IT 168169-96-8P 168169-98-0P 347849-97-2P 347850-01-5P 347850-22-0P 347850-27-5P 347850-28-6P **347885-67-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3-tetrazolylpyrrolidines as cAMP-specific phosphodiesterase inhibitors)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

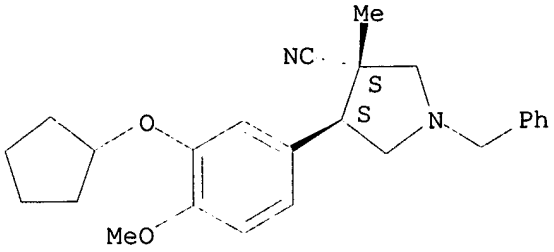
RE

(1) Anon; DATABASE MEDLINE
(2) Makino, E; J PHARM PHARMACOL 1990, V42(4), P236 HCAPLUS
(3) Matousovic, K; JOURNAL OF LABORATORY AND CLINICAL MEDICINE 1997, V130(5), P487 HCAPLUS
(4) Segarra, V; BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1998, V8(5), P505 HCAPLUS
(5) Smithkline Beecham Corp; WO 9703945 A 1997 HCAPLUS

IT **347885-67-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 3-tetrazolylpyrrolidines as cAMP-specific phosphodiesterase inhibitors)
RN 347885-67-0 HCAPLUS
CN 3-Pyrrolidinecarbonitrile, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:489383 HCAPLUS
DN 135:76790
TI Preparation of pyrrolidine derivatives as cyclic AMP-specific phosphodiesterase inhibitors
IN Martins, Timothy J.; Fowler, Kerry W.; Odingo, Joshua; Kesicki, Edward A.; Oliver, Amy; Burgess, Laurence E.; Gaudino, John J.; Jones, Zachary S.; Newhouse, Bradley J.; Schlachter, Stephen
PA Icos Corporation, USA
SO PCT Int. Appl., 551 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D295-20
ICS C07D295-18; C07D417-06; C07D401-12; C07D295-14; C07D405-06; C07D401-04; C07D417-12; C07D403-12; C07D401-06; C07D407-12; C07D413-12; C07D407-06; C07D409-12; A61K031-40
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001047905	A1	20010705	WO 2000-US32401	20001128
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6258833	B1	20010710	US 1999-471846	19991223
	EP 1242400	A1	20020925	EP 2000-987999	20001128
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 6458787	B1	20021001	US 2001-847424	20010502
	NO 2002003008	A	20020820	NO 2002-3008	20020621
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OS MARPAT 135:76790
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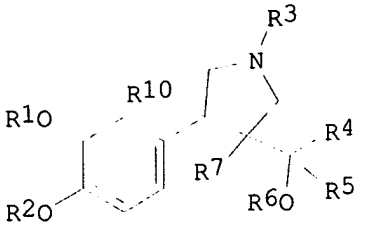

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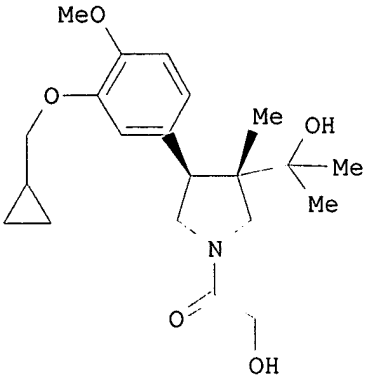

II

AB The title compds. [I; R1 = H, alkyl, aryl, etc.; R2 = H, Me, halo-substituted methyl; R3 = CO2R7, COR7, NHCO2R7, etc.; R4 = H, alkyl, haloalkyl, etc.; R5 = H, alkyl, alkynyl, etc.; R6 = H, alkyl, COR7; R7 = alkyl, cycloalkyl, heteroaryl, etc.; R10 = H, alkyl, aryl, etc.] that are potent and selective inhibitors of PDE4, and are useful in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, were prepd. E.g., a multi-step synthesis of II was presented. Biol. data (e.g., IC50 against PDE4 and EC50 against TNF.alpha. release) for compds. I were given.

ST pyrrolidine prepn phosphodiesterase adenosine cyclic monophosphate specific inhibitor; tumor necrosis factor alpha pyrrolidine prepn

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

IT 9036-21-9, phosphodiesterase IV
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(IV; prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

IT 347843-77-0P 347843-81-6P 347843-95-2P 347843-99-6P 347844-22-8P
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RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

IT 347843-65-6P 347843-67-8P 347843-69-0P 347843-71-4P 347843-73-6P
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RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

IT 60-12-8, 2-Phenylethanol 78-93-3, 2-Butanone, reactions 98-52-2, 4-tert-Butyl-cyclohexanol 100-46-9, Benzylamine, reactions 101-55-3 103-63-9, 2-Phenethyl bromide 104-52-9, 3-Phenylpropyl chloride 106-96-7, Propargyl bromide 107-19-7, Propargyl alcohol 109-01-3, 1-Methylpiperazine 109-04-6, 2-Bromopyridine 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 327-56-0, D-Norleucine 332-48-9 453-20-3, 3-Hydroxytetrahydrofuran 455-13-0, 4-Iodobenzotrifluoride 497-36-9, endo-Norborneol 500-22-1, Pyridine-3-carboxaldehyde 589-91-3, 4-Methylcyclohexanol 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 623-03-0, 4-Chlorobenzonitrile 624-95-3, 3,3-Dimethyl-1-butanol 626-55-1, 3-Bromopyridine 766-00-7, 2-Cyclopentylethanol 767-05-5, 3-Cyclopentylpropan-1-ol 768-22-9, Indene oxide 825-51-4 872-85-5, Pyridine-4-carboxaldehyde 1003-03-8, Cyclopentylamine 1118-68-9, N,N-Dimethylglycine 1121-60-4, Pyridine-2-carboxaldehyde 1138-80-3, N-Benzyloxycarbonylglycine 1168-87-2 1504-58-1, 3-Phenyl-2-propyn-1-ol 1638-63-7, O-Acetyl mandelic acid chloride 1716-42-3, 1-(3-Chloropropoxy)-4-fluorobenzene 1738-86-9 1738-87-0 1849-02-1, 2-Chloro-N-methylbenzimidazole 2344-70-9, 4-Phenyl-2-butanol 2433-14-9, [1,1'-Bicyclohexyl]-4-ol 2495-35-4, Benzyl acrylate 2566-44-1, 2-Cyclopropylethanol 2578-84-9 2578-85-0 2746-14-7, 1-Methylcyclopropanemethanol 3034-53-5, 2-Bromothiazole 3047-32-3 3313-85-7, (Bicyclo[3.1.0]hex-6-yl)methanol 3355-28-0, 1-Bromo-2-butyne 3642-91-9 3655-05-8 3699-66-9, Triethyl 2-phosphonopropionate 4254-29-9, 2-Indanol 4467-55-4 4830-93-7, 1-Chloro-4-phenylbutane 5437-45-6, Benzyl bromoacetate 5781-53-3, Methyl oxalyl chloride 6226-39-7, (Bicyclo[4.1.0]hept-7-yl)methanol 6346-05-0, 3-Benzyloxy-4-methoxybenzaldehyde 7051-34-5, Bromomethylcyclopropane 7326-19-4 10512-93-3 10553-78-3 13748-90-8 13831-31-7 14300-33-5, Dicyclopropylcarbinol 15030-72-5, N-Carbobenzyloxy-2-methylalanine 15733-63-8, 1-Chloro-5-phenylpentane 15833-61-1, (Tetrahydrofuran-3-yl)methanol 16133-25-8, 3-Pyridinesulfonyl chloride 17347-61-4, 2,2-Dimethylsuccinic anhydride 17623-96-0 17994-25-1, 1-Hydroxycyclopropanecarboxylic acid 18217-00-0, 1-(2-Chloroethyl)-4-methoxybenzene 19810-31-2, Benzyloxyacetyl chloride 20312-36-1 24181-97-3 27167-53-9 29667-46-7 30129-18-1 31062-20-1 31729-66-5, (1-Phenylcyclopropyl)methanol 32222-45-0 34841-06-0, 3-Bromo-4-methoxybenzaldehyde 35272-15-2 36394-75-9, (S)-2-Acetoxypropionyl chloride 37729-18-3, [1,1'-Biphenyl]-4-ethanol 38939-83-2, 2-Acetoxypropionyl chloride 40635-66-3, 2-Acetoxyisobutyryl chloride 47173-80-8, N-tert-Butoxycarbonyl-O-benzyl-D-serine 52235-17-3 53636-19-4 56539-66-3, 3-Methoxy-3-methylbutanol 57070-76-5 59115-90-1, (1-Phenylcyclopentyl)methanol 60656-87-3, Benzyloxyacetaldehyde 62965-10-0 67387-76-2, 3-Cyclopentyloxy-4-methoxybenzaldehyde 69595-02-4, Tetrahydrofuran-3-carbonyl chloride 69901-85-5 71432-55-8 86087-23-2, (S)-3-Hydroxytetrahydrofuran 86087-24-3 90192-47-5 90319-52-1, (R)-Phenyloxazolidinone 93102-05-7 97673-82-0 116561-26-3 124655-17-0 130990-25-9 173258-94-1 204119-59-5 205880-21-3 347845-00-5 347845-08-3 347848-91-3 347850-64-0 347850-65-1 347850-66-2 347850-67-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

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347850-57-1P 347850-58-2P 347850-59-3P 347850-60-6P 347850-61-7P
347850-62-8P 347850-63-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

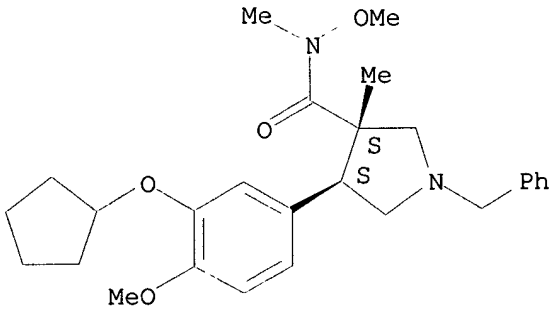
RE

(1) Glaxo Inc; WO 9508534 A 1995 HCAPLUS
(2) Mitsubishi Chem Corp; EP 0671389 A 1995 HCAPLUS
(3) Schering Ag; WO 9725312 A 1997 HCAPLUS
(4) Yoshitomi Pharmaceutical; DE 2409646 A 1974 HCAPLUS

IT **347850-24-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolidine derivs. as cAMP-specific phosphodiesterase inhibitors)

RN 347850-24-2 HCAPLUS
CN 3-Pyrrolidinecarboxamide, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N-methoxy-N,3-dimethyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



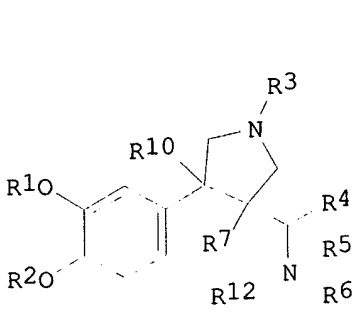
L11 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:489364 HCAPLUS
DN 135:92536
TI Preparation of pyrrolidines which inhibit cAMP-specific PDE
IN Martins, Timothy J.; Fowler, Kerry W.; Odingo, Joshua; Burgess, Laurence E.; Schlachter, Stephen T.
PA Icos Corp., USA
SO PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DT Patent
LA English

KATHLEEN FULLER EIC 1700/PARKER LAW 308-4290

IC ICM C07D207-09
ICS A61K031-40; A61P029-00
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001047879	A1	20010705	WO 2000-US34116	20001215
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6376489	B1	20020423	US 2000-731591	20001207
	EP 1244619	A1	20021002	EP 2000-984450	20001215
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2002169196	A1	20021114	US 2002-77154	20020215
	NO 2002003009	A	20020819	NO 2002-3009	20020621
PRAI	US 1999-172023P	P	19991223		
	US 2000-731591	A1	20001207		
	WO 2000-US34116	W	20001215		

OS MARPAT 135:92536
GI



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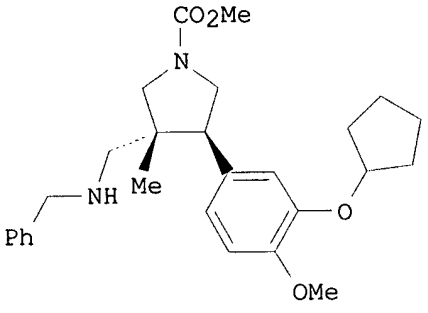

II

AB The title compds. [I; R1 = alkyl, aryl, heteroaryl, etc.; R2 = H, Me, halomethyl; R3 = CO2R7, COR7, alkyl, etc.; R4 = H, alkyl, haloalkyl, etc.; R5 = H, alkyl, alkynyl, etc.; R6, R12 = H, alkyl, aralkyl, etc.; R7 = alkyl, heteroaryl, aryl, etc.; R10 = H, alkyl, haloalkyl, etc.] that are potent and selective inhibitors of PDE4, and are useful in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, were prepd. E.g., a multi-step synthesis of II which showed IC50 of 1400.0x10-9 M against PDE4, and IC50 of 775.5x10-9 M against TNF.alpha. formation, was given.

ST pyrrolidine prepn phosphodiesterase adenosine cyclic phosphate specific inhibitor; tumor necrosis factor alpha pyrrolidine prepn

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL

(Biological study)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)
IT **348077-95-2P 348077-96-3P 348077-97-4P**
348077-98-5P 348077-99-6P 348078-00-2P
348078-01-3P 348078-02-4P 348078-03-5P
348078-04-6P 348078-05-7P 348078-06-8P
348078-07-9P 348078-08-0P 348078-09-1P
348078-10-4P 348078-11-5P 348078-12-6P
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348078-16-0P 348078-17-1P 348078-18-2P
348078-19-3P 348078-20-6P 348078-21-7P
348078-22-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)
IT 9036-21-9, phosphodiesterase IV
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)
IT 100-46-9, Benzylamine, reactions 3699-66-9 67387-76-2 90319-52-1, (R)-4-Phenyloxazolidin-2-one 93102-05-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)
IT 168169-96-8P 168169-98-0P 347849-97-2P 347850-01-5P 347850-22-0P 347850-27-5P 347850-28-6P 348078-23-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Glaxo Inc; WO 9508534 A 1995 HCAPLUS
(2) Mitsubishi Chem Corp; EP 0671389 A 1995 HCAPLUS
(3) Nakanishi, M; US 3935217 A 1976 HCAPLUS
(4) Schering Ag; WO 9725312 A 1997 HCAPLUS
(5) Smithkline Beecham Corp; WO 9219594 A 1992 HCAPLUS
IT **348077-95-2P 348077-96-3P 348077-97-4P**
348077-98-5P 348077-99-6P 348078-00-2P
348078-01-3P 348078-02-4P 348078-03-5P
348078-04-6P 348078-05-7P 348078-06-8P
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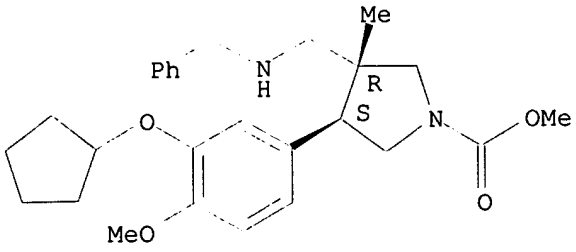
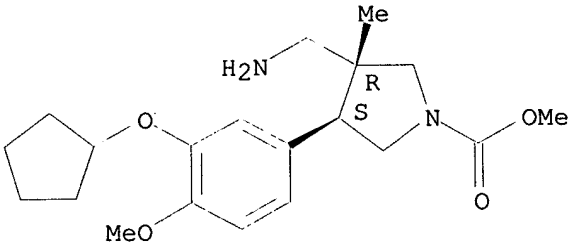
348078-16-0P 348078-17-1P 348078-18-2P
348078-19-3P 348078-20-6P 348078-21-7P
348078-22-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrolidines which inhibit cAMP-specific PDE)
RN 348077-95-2 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[[(phenylmethyl)amino]methyl]-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



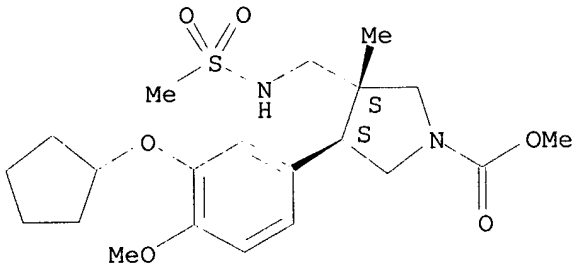
RN 348077-96-3 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



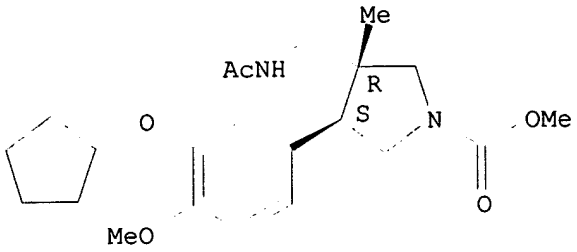
RN 348077-97-4 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[[(methylsulfonyl)amino]methyl]-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



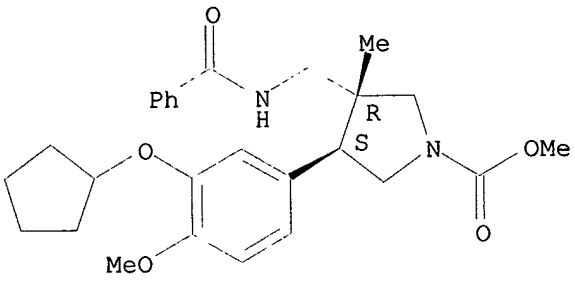
RN 348077-98-5 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[(acetylamino)methyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



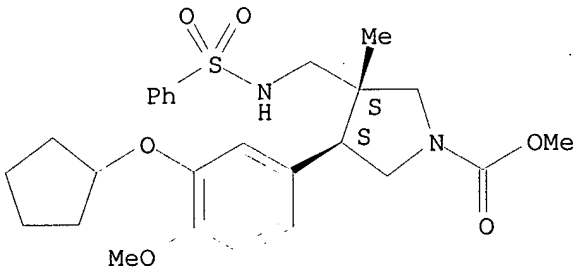
RN 348077-99-6 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[(benzoylamino)methyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



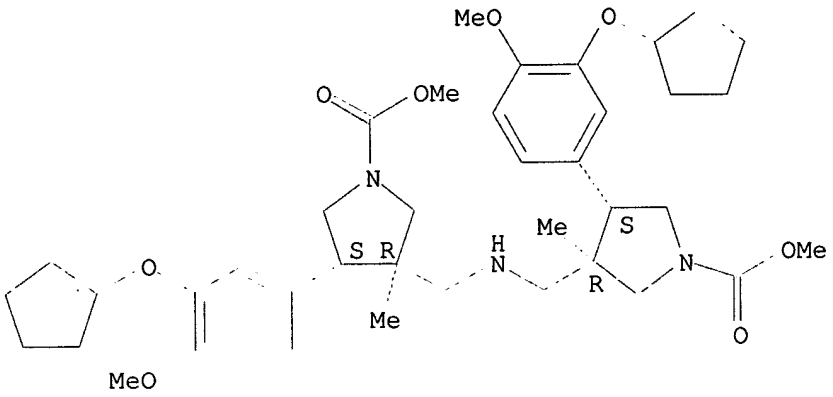
RN 348078-00-2 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[[(phenylsulfonyl)amino]methyl]-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



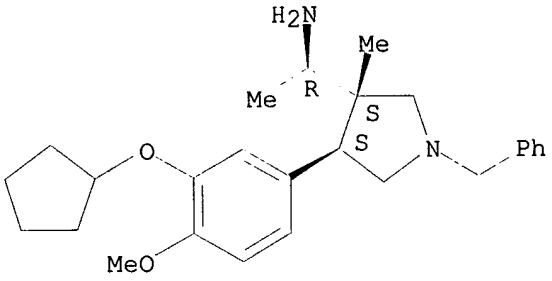
RN 348078-01-3 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3,3'-[iminobis(methylene)]bis[4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, dimethyl ester, (3R,3'R,4S,4'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



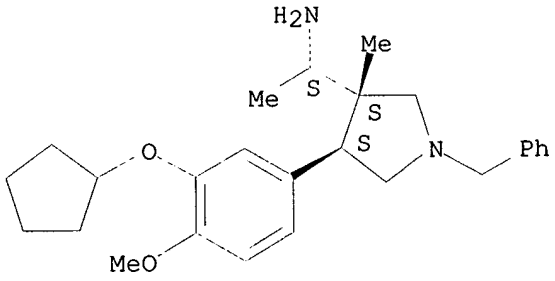
RN 348078-02-4 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-.alpha.,3-dimethyl-1-(phenylmethyl)-, (.alpha.R,3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



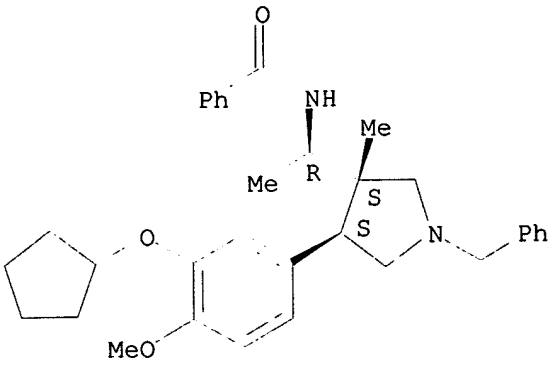
RN 348078-03-5 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-.alpha.,3-dimethyl-1-(phenylmethyl)-, (.alpha.S,3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



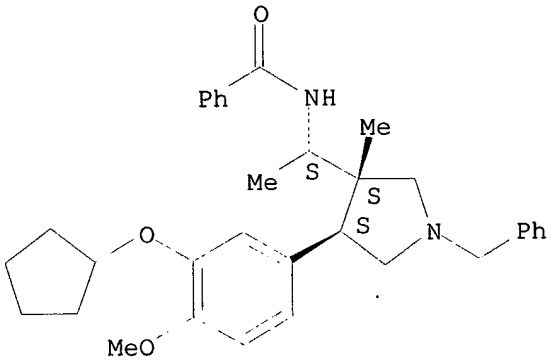
RN 348078-04-6 HCAPLUS
CN Benzamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



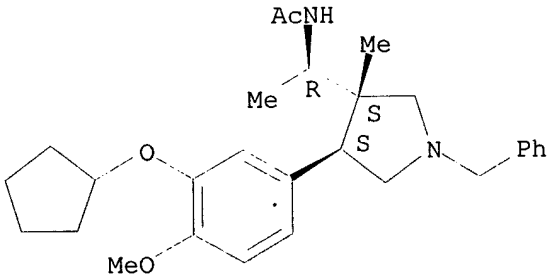
RN 348078-05-7 HCAPLUS
CN Benzamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



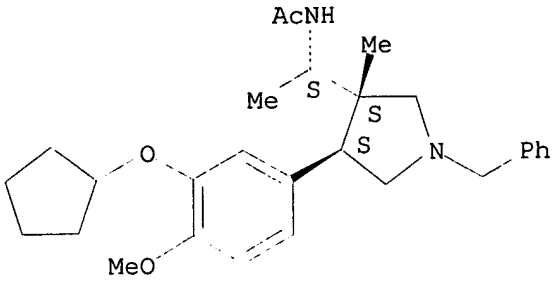
RN 348078-06-8 HCAPLUS
CN Acetamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



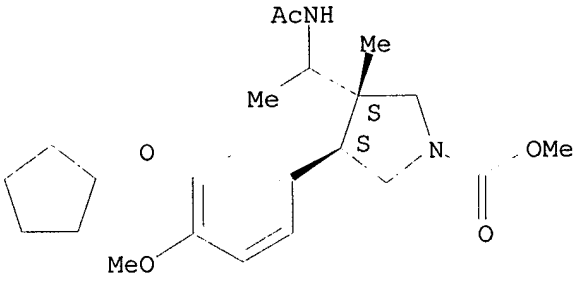
RN 348078-07-9 HCAPLUS
CN Acetamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



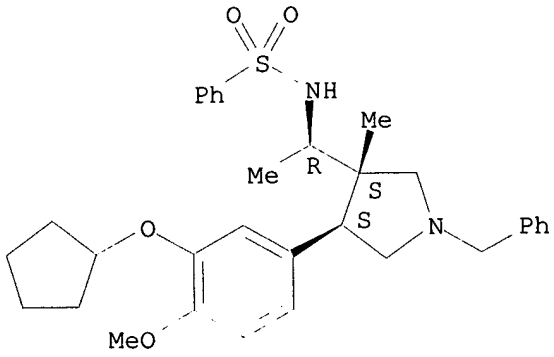
RN 348078-08-0 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[1-(acetylamino)ethyl]-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



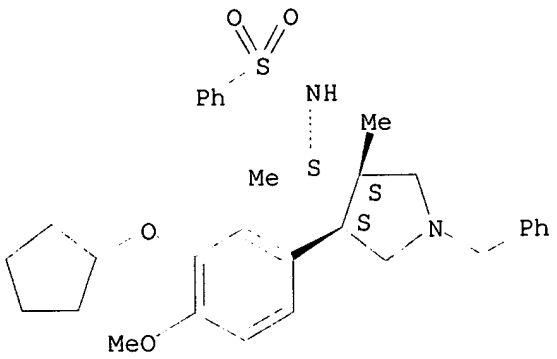
RN 348078-09-1 HCAPLUS
CN Benzenesulfonamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



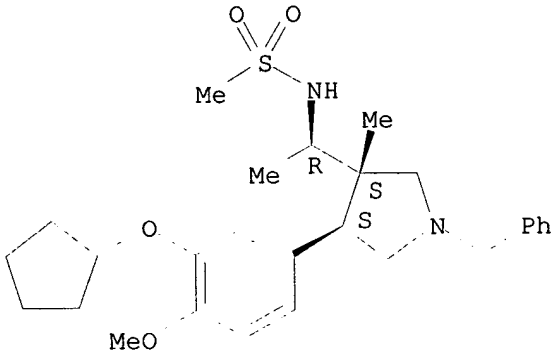
RN 348078-10-4 HCAPLUS
CN Benzenesulfonamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



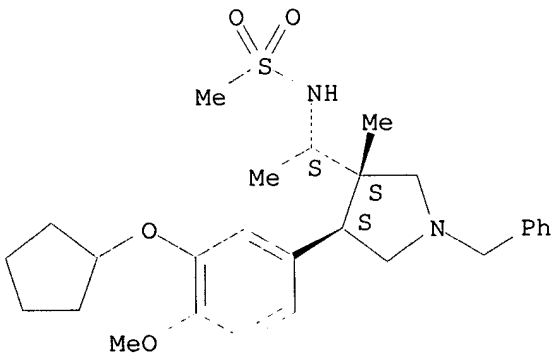
RN 348078-11-5 HCAPLUS
CN Methanesulfonamide, N-[(1R)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



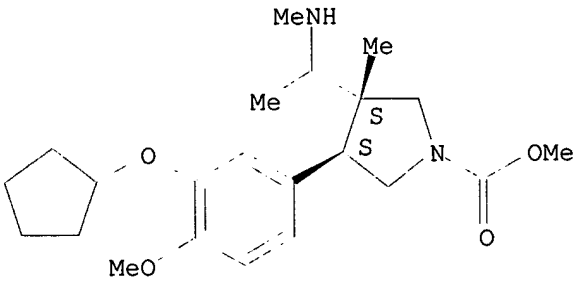
RN 348078-12-6 HCAPLUS
CN Methanesulfonamide, N-[(1S)-1-[(3S,4S)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-(phenylmethyl)-3-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



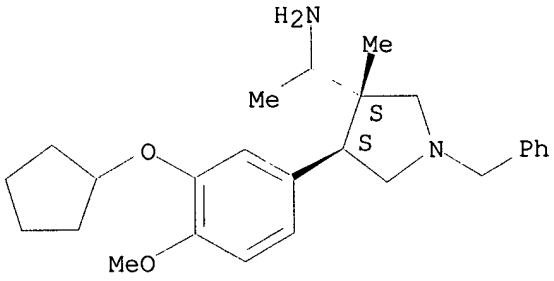
RN 348078-13-7 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[1-(methylamino)ethyl]-, methyl ester, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



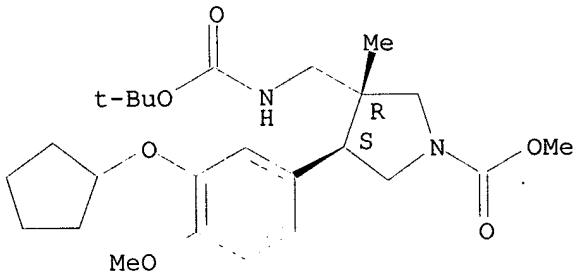
RN 348078-14-8 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-.alpha.,3-dimethyl-1-(phenylmethyl)-, (3S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



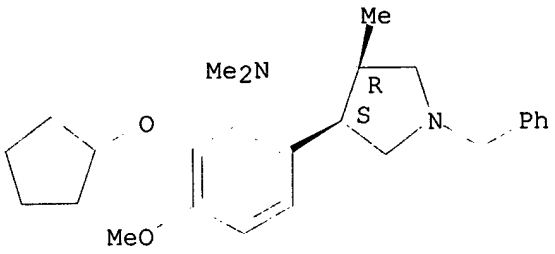
RN 348078-15-9 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



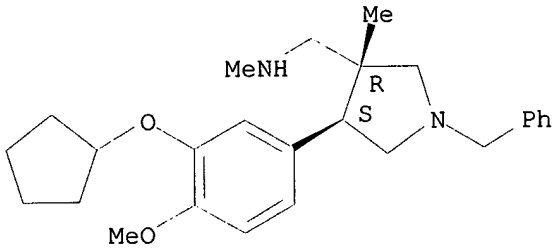
RN 348078-16-0 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N,N,3-trimethyl-1-(phenylmethyl)-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



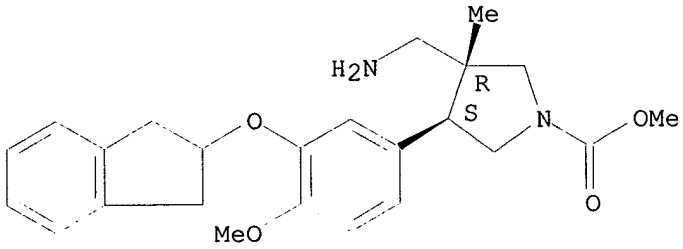
RN 348078-17-1 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N,3-dimethyl-1-(phenylmethyl)-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



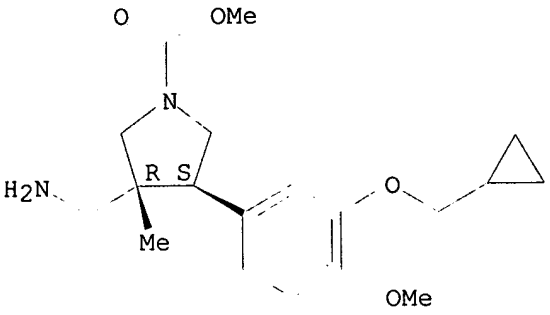
RN 348078-18-2 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminomethyl)-4-[3-[(2,3-dihydro-1H-inden-2-yl)oxy]-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



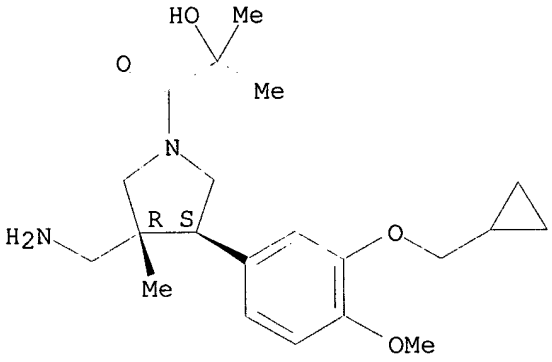
RN 348078-19-3 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-(aminomethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methyl-, methyl ester, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



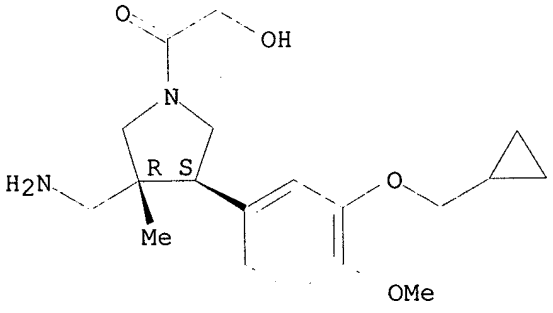
RN 348078-20-6 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-1-(2-hydroxy-2-methyl-1-oxopropyl)-3-methyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



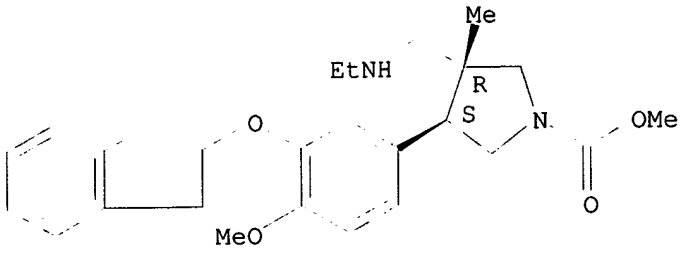
RN 348078-21-7 HCAPLUS
CN 3-Pyrrolidinemethanamine, 4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-1-(hydroxyacetyl)-3-methyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 348078-22-8 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-[(2,3-dihydro-1H-inden-2-yl)oxy]-4-methoxyphenyl]-3-[(ethylamino)methyl]-3-methyl-, methyl ester, (3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:472663 HCAPLUS
DN 135:61233
TI Preparation and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents
IN Fowler, Kerry W.; Oliver, Amy; Odingo, Joshua
PA Icos Corp., USA
SO PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D207-09
ICS A61K031-40; A61P029-00; A61P019-02
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 7, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001046136	A1	20010628	WO 2000-US42316	20001128
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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	US 6348602	B1	20020219	US 2000-716024	20001117
	EP 1242371	A1	20020925	EP 2000-992155	20001128
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	US 2002065302	A1	20020530	US 2001-16910	20011214
	US 6500856	B2	20021231		
PRAI	US 1999-171955P	P	19991223		
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OS MARPAT 135:61233
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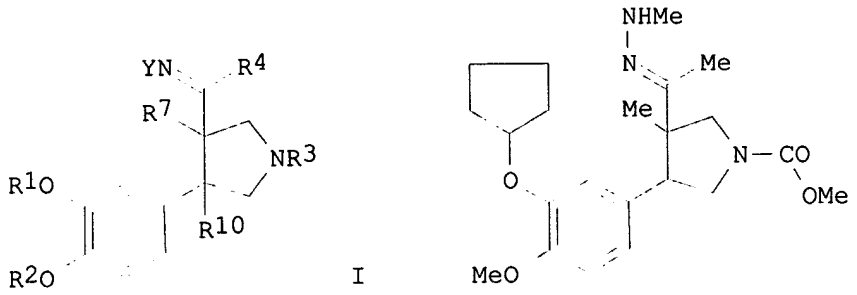


AB Pyrrolidine hydrazones and oximes, such as I [Y = OR5, NR5R6; R1 = alkyl, arylalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkynyl, etc.; R2 = H, Me, halomethyl; R3 = carboxyl, acyl, amido, aryl, heteroaryl, amidinyl; R4 = H, alkyl, haloalkyl, cycloalkyl, aryl; R5, R6 = H, alkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, etc.; R7 = alkyl, aryl, aminoalkyl, alkoxyalkyl, etc.; R10 = H, CH2OH, CHO, CN, NO2, alkyl, haloalkyl, cycloalkyl, aryl, acyl, sulfonyl, etc.], were prepd. as potent and selective inhibitors of PDE4 for use in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders. Thus, pyrrolidine hydrazone II was prepd. by reaction of the corresponding ketone with methylhydrazine by heating with a catalytic amt. of AcOH in MeOH for 36 h. The prepd. pyrrolidine hydrazones and oximes were tested for PDE4 and TNF.alpha. inhibiting activity.

ST pyrrolidine hydrazone oxime prepn PDE4 inhibitor; phosphodiesterase inhibitor pyrrolidine hydrazone oxime prepn; antiinflammatory agent pyrrolidine hydrazone oxime prepn; tumor necrosis factor inhibitor pyrrolidine hydrazone oxime prepn

IT Anti-inflammatory agents
(nonsteroidal; prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

IT **346408-85-3P 346408-86-4P 346408-87-5P 346408-88-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

IT 9036-21-9, CAMP-specific phosphodiesterase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

IT 60-34-4, Methylhydrazine 78-93-3, 2-Butanone, reactions 79-22-1 621-59-0 4254-29-9 5470-11-1, Hydroxylamine hydrochloride 93102-05-7 346408-89-7 346408-90-0
RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

IT 115898-38-9P 346408-91-1P 346408-92-2P 346408-93-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

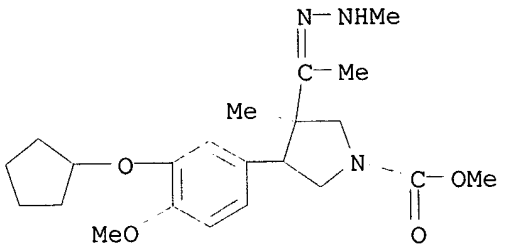
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Glaxo Inc; WO 9508534 A 1995 HCAPLUS
(2) Mitsubishi Chem Corp; EP 0671389 A 1995 HCAPLUS
(3) Smithkline Beecham Corp; WO 9219594 A 1992 HCAPLUS

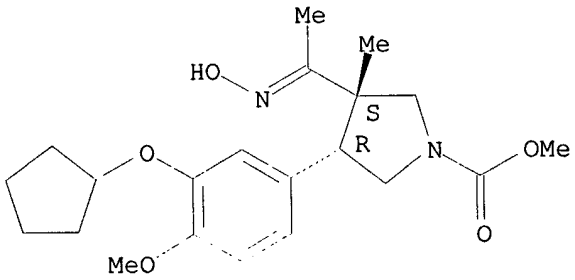
IT **346408-85-3P 346408-86-4P 346408-87-5P 346408-88-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidine hydrazones and oximes as cAMP-specific phosphodiesterase inhibitors for pharmaceutical use as anti-inflammatory agents)

RN 346408-85-3 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-3-[1-(methylhydrazono)ethyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 346408-86-4 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[1-(hydroxyimino)ethyl]-3-methyl-, methyl ester, (3S,4R)- (9CI) (CA INDEX NAME)

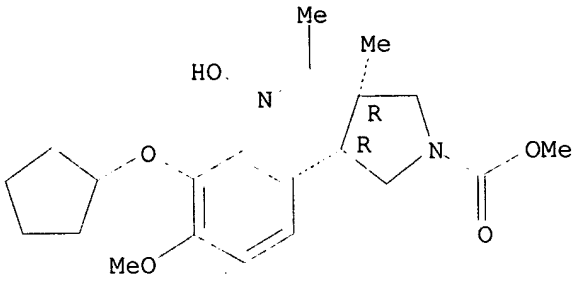
Absolute stereochemistry.
Double bond geometry unknown.



RN 346408-87-5 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[1-

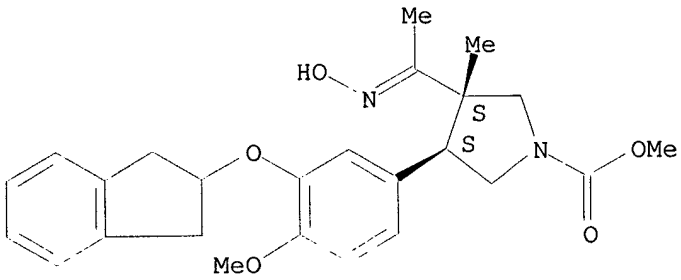
(hydroxyimino)ethyl]-3-methyl-, methyl ester, (3R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 346408-88-6 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 4-[3-[(2,3-dihydro-1H-inden-2-yl)oxy]-4-methoxyphenyl]-3-[1-(hydroxyimino)ethyl]-3-methyl-, methyl ester, (3R,4R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



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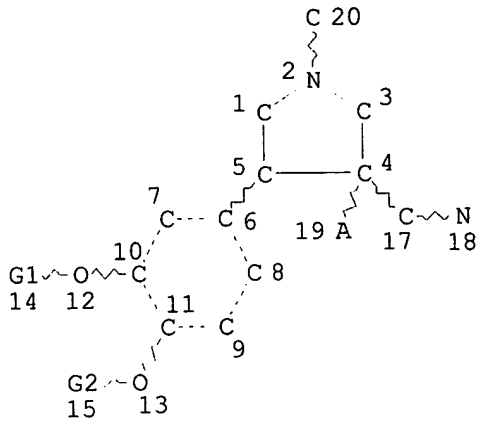

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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L12 0 SEA FILE=HCAOLD ABB=ON L10

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